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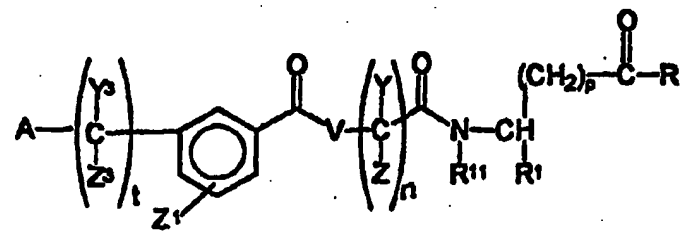
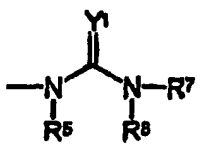
(57) Abstract

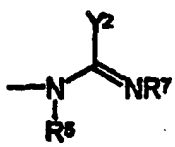
The present invention relates to a class of compounds represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein A is (a) or (b) or (c) or (d) pharmaceutical compositions thereof and methods of using such compounds and compositions as $\alpha_v\beta_3$ integrin antagonists.



(I)



(a)



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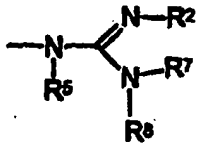

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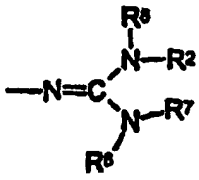


(d)

PCT/US01/50619 WEST

META-GUANIDINE, UREA, THIOUREA OR AZACYCLIC AMINO BENZOIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

The present application claims priority under 35 USC §119(e) of United States provisional application Serial No. 60/003,277 filed August 30, 1995.

Field of the Invention

The present invention relates to pharmaceutical agents (compounds) which are useful as $\alpha_v\beta_3$ integrin antagonists and as such are useful in pharmaceutical compositions and in methods for treating conditions mediated by $\alpha_v\beta_3$ by inhibiting or antagonizing $\alpha_v\beta_3$ integrins.

Background of the Invention

Integrins are a group of cell surface glycoproteins which mediate cell adhesion and therefore are useful mediators of cell adhesion interactions which occur during various biological processes. Integrins are heterodimers composed of noncovalently linked α and β polypeptide subunits. Currently eleven different α subunits have been identified and six different β subunits have been identified. The various α subunits can combine with various β subunits to form distinct integrins.

The integrin identified as $\alpha_v\beta_3$ (also known as the vitronectin receptor) has been identified as an integrin which plays a role in various conditions or disease states including tumor metastasis, solid tumor growth (neoplasia), osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, angiogenesis, including tumor angiogenesis, retinopathy, arthritis, including rheumatoid arthritis, periodontal disease, psoriasis and smooth muscle cell migration (e.g. restenosis). Additionally, it has been found that such agents would be useful as antivirals, antifungals and antimicrobials. Thus, compounds which selectively

inhibit or antagonize $\alpha_v\beta_3$ would be beneficial for treating such conditions.

It has been shown that the $\alpha_v\beta_3$ integrin and other α_v containing integrins bind to a number of Arg-Gly-Asp (RGD) containing matrix macromolecules. Compounds containing the RGD sequence mimic extracellular matrix ligands so as to bind to cell surface receptors. However, it is also known that RGD peptides in general are non-selective for RGD dependent integrins. For example, most RGD peptides which bind to $\alpha_v\beta_3$ also bind to $\alpha_v\beta_5$, $\alpha_v\beta_1$ and $\alpha_{IIb}\beta_3$. Antagonism of platelet $\alpha_{IIb}\beta_3$ (also known as the fibrinogen receptor) is known to block platelet aggregation in humans. In order to avoid bleeding side-effects when treating the conditions or disease states associated with the integrin $\alpha_v\beta_3$, it would be beneficial to develop compounds which are selective antagonists of $\alpha_v\beta_3$ as opposed to $\alpha_{IIb}\beta_3$.

Tumor cell invasion occurs by a three step process: 1) tumor cell attachment to extracellular matrix; 2) proteolytic dissolution of the matrix; and 3) movement of the cells through the dissolved barrier. This process can occur repeatedly and can result in metastases at sites distant from the original tumor.

Seftor et al. (Proc. Natl. Acad. Sci. USA, Vol. 89 (1992) 1557-1561) have shown that the $\alpha_v\beta_3$ integrin has a biological function in melanoma cell invasion. Montgomery et al., (Proc. Natl. Acad. Sci. USA, Vol. 91 (1994) 8856-60) have demonstrated that the integrin $\alpha_v\beta_3$ expressed on human melanoma cells promotes a survival signal, protecting the cells from apoptosis. Mediation of the tumor cell metastatic pathway by interference with the $\alpha_v\beta_3$ integrin cell adhesion receptor to impede tumor metastasis would be beneficial.

Brooks et al. (Cell, Vol. 79 (1994) 1157-1164) have demonstrated that antagonists of $\alpha_v\beta_3$ provide a therapeutic approach for the treatment of neoplasia (inhibition of solid tumor growth) since systemic

administration of $\alpha_v\beta_3$ antagonists causes dramatic regression of various histologically distinct human tumors.

The adhesion receptor integrin $\alpha_v\beta_3$ was identified as a marker of angiogenic blood vessels in chick and man and therefore such receptor plays a critical role in angiogenesis or neovascularization. Angiogenesis is characterized by the invasion, migration and proliferation of smooth muscle and endothelial cells. Antagonists of $\alpha_v\beta_3$ inhibit this process by selectively promoting apoptosis of cells in neovasculature. The growth of new blood vessels, or angiogenesis, also contributes to pathological conditions such as diabetic retinopathy (Adonis et al., Amer. J. Ophthal., Vol. 118, (1994) 445-450) and rheumatoid arthritis (Peacock et al., J. Exp. Med., Vol. 175, (1992), 1135-1138). Therefore, $\alpha_v\beta_3$ antagonists would be useful therapeutic targets for treating such conditions associated with neovascularization (Brooks et al., Science, Vol. 264, (1994), 569-571).

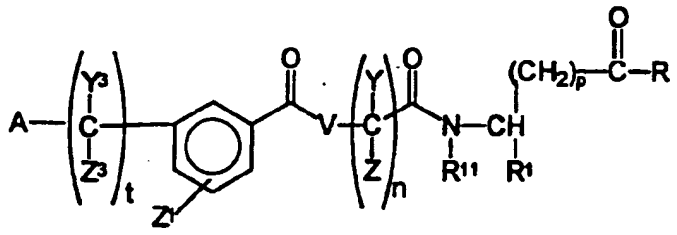
It has been reported that the cell surface receptor $\alpha_v\beta_3$ is the major integrin on osteoclasts responsible for attachment to bone. Osteoclasts cause bone resorption and when such bone resorbing activity exceeds bone forming activity it results in osteoporosis (a loss of bone), which leads to an increased number of bone fractures, incapacitation and increased mortality. Antagonists of $\alpha_v\beta_3$ have been shown to be potent inhibitors of osteoclastic activity both *in vitro* [Sato et al., J. Cell. Biol., Vol. 111 (1990) 1713-1723] and *in vivo* [Fisher et al., Endocrinology, Vol. 132 (1993) 1411-1413]. Antagonism of $\alpha_v\beta_3$ leads to decreased bone resorption and therefore restores a normal balance of bone forming and resorbing activity. Thus it would be beneficial to provide antagonists of osteoclast $\alpha_v\beta_3$ which are effective inhibitors of bone resorption and therefore are useful in the treatment or prevention of osteoporosis.

The role of the $\alpha_v\beta_3$ integrin in smooth muscle cell migration also makes it a therapeutic target for prevention or inhibition of neointimal hyperplasia which is a leading cause of restenosis after vascular procedures (Choi et al., J. Vasc. Surg. Vol. 19(1) (1994) 125-34). Prevention or inhibition of neointimal hyperplasia by pharmaceutical agents to prevent or inhibit restenosis would be beneficial.

White (Current Biology, Vol. 3(9)(1993) 596-599) has reported that adenovirus uses $\alpha_v\beta_3$ for entering host cells. The integrin appears to be required for endocytosis of the virus particle and may be required for penetration of the viral genome into the host cell cytoplasm. Thus compounds which inhibit $\alpha_v\beta_3$ would find usefulness as antiviral agents.

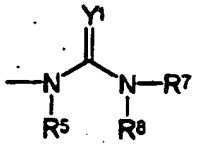
Summary of the Invention

The present invention relates to a class of compounds represented by the Formula I



or a pharmaceutically acceptable salt thereof, wherein

A is



wherein Y^1 is selected from the group consisting of $N-R^2$, O, and S;

R^2 is selected from the group consisting of H; alkyl; aryl; hydroxy; alkoxy; cyano; nitro; amino; alkenyl; alkynyl; amido; alkylcarbonyl; arylcarbonyl; alkoxycarbonyl; aryloxycarbonyl; haloalkylcarbonyl; haloalkoxycarbonyl; alkylthiocarbonyl; arylthiocarbonyl; acyloxymethoxycarbonyl; alkyl optionally substituted with one or more substituent selected from lower alkyl, halogen, hydroxyl, haloalkyl, cyano, nitro, carboxyl, amino, alkoxy, aryl or aryl optionally substituted with one or more halogen, haloalkyl, lower alkyl, alkoxy, cyano, alkylsulfonyl, alkylthio, nitro, carboxyl, amino, hydroxyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles, or fused monocyclic heterocycles; aryl optionally substituted with one or more substituent selected from halogen, haloalkyl, hydroxy, lower alkyl, alkoxy, methylenedioxy, ethylenedioxy, cyano, nitro, alkylthio, alkylsulfonyl, sulfonic acid, sulfonamide, carboxyl derivatives, amino, aryl, fused aryl, monocyclic heterocycles and fused monocyclic heterocycle; monocyclic heterocycles; and monocyclic heterocycles optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy, amino, nitro, hydroxy, carboxyl derivatives, cyano, alkylthio, alkylsulfonyl, sulfonic acid, sulfonamide, aryl or fused aryl; or

R^2 taken together with R^7 forms a 4-12 membered dinitrogen containing heterocycle optionally substituted with one or more substituent selected from the group consisting of lower alkyl, hydroxy,

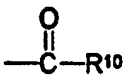
keto, alkoxy, halo, phenyl, amino, carboxyl or carboxyl ester, and fused phenyl;

or R^2 taken together with R^7 forms a 5 membered heteroaromatic ring optionally substituted with one or more substituent selected from lower alkyl, phenyl and hydroxy;

or R^2 taken together with R^7 forms a 5 membered heteroaromatic ring fused with a phenyl group;

R^7 (when not taken together with R^2) and R^8 are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; aralkyl; amino; alkylamino; hydroxy; alkoxy; arylamino; amido, alkylcarbonyl, arylcarbonyl; alkoxycarbonyl; aryloxy; aryloxycarbonyl; haloalkylcarbonyl; haloalkoxycarbonyl; alkylthiocarbonyl; arylthiocarbonyl; acyloxymethoxycarbonyl; cycloalkyl; bicycloalkyl; aryl; acyl; benzoyl; alkyl optionally substituted with one or more substituent selected from lower alkyl, halogen, hydroxy, haloalkyl, cyano, nitro, carboxyl derivatives, amino, alkoxy, thio, alkylthio, sulfonyl, aryl, aralkyl, aryl optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkylthio, thio, hydroxy, cyano, nitro, carboxyl derivatives, aryloxy, amido, acylamino, amino, alkylamino, dialkylamino, trifluoroalkoxy, trifluoromethyl, sulfonyl, alkylsulfonyl, haloalkylsulfonyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles, fused monocyclic heterocycles; aryl optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy,

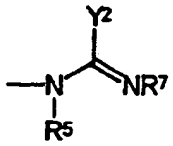
methylenedioxy, ethylenedioxy, alkylthio, haloalkylthio, thio, hydroxy, cyano, nitro, carboxyl derivatives, aryloxy, amido, acylamino, amino, alkylamino, dialkylamino, trifluoroalkoxy, trifluoromethylsulfonyl, alkylsulfonyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles, or fused monocyclic heterocycles; monocyclic heterocycles; monocyclic heterocycles optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy, aryloxy, amino, nitro, hydroxy, carboxyl derivatives, cyano, alkylthio, alkylsulfonyl, aryl, fused aryl; monocyclic and bicyclic heterocyclicalkyls; $-SO_2R^{10}$ wherein R^{10} is selected from the group consisting of alkyl, aryl and monocyclic heterocycles, all optionally substituted with one or more substituent selected from the group consisting of halogen, haloalkyl, alkyl, alkoxy, cyano, nitro, amino, acylamino, trifluoroalkyl, amido, alkylaminosulfonyl, alkylsulfonyl, alkylsulfonylamino, alkylamino, dialkylamino, trifluoromethylthio, trifluoroalkoxy, trifluoromethylsulfonyl, aryl, aryloxy, thio, alkylthio, and monocyclic heterocycles; and

 wherein R^{10} is defined above;

or NR^7 and R^8 taken together form a 4-12 membered mononitrogen containing monocyclic or bicyclic ring optionally substituted with one or more substituent selected from lower alkyl, carboxyl derivatives, aryl or hydroxy and wherein said ring optionally contains a heteroatom selected from the group consisting of O, N and S;

R^5 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, benzyl, and phenethyl;

or

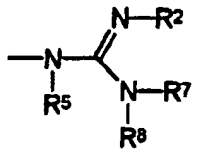
A is 

wherein Y^2 is selected from the group consisting of alkyl; cycloalkyl; bicycloalkyl; aryl; monocyclic heterocycles; alkyl optionally substituted with aryl which can also be optionally substituted with one or more substituent selected from halo, haloalkyl, alkyl, nitro, hydroxy, alkoxy, aryloxy, aryl, or fused aryl; aryl optionally substituted with one or more substituent selected from halo, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, fused aryl, nitro, methylenedioxy, ethylenedioxy, or alkyl; alkynyl; alkenyl; $-S-R^9$ and $-O-R^9$ wherein R^9 is selected from the group consisting of H; alkyl; aralkyl; aryl; alkenyl; and alkynyl; or R^9 taken together with R^7 forms a 4-12 membered mononitrogen and monosulfur or monooxygen containing heterocyclic ring optionally substituted with lower alkyl, hydroxy, keto, phenyl, carboxyl or carboxyl ester, and fused phenyl; or R^9 taken together with R^7 is thiazole; oxazole; benzoxazole; or benzothiazole; and

R^5 and R^7 are as defined above;

or Y^2 (when Y^2 is carbon) taken together with R^7 forms a 4-12 membered mononitrogen or dinitrogen containing ring optionally substituted with alkyl, aryl, keto or hydroxy;

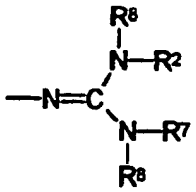
or A is



where R^2 and R^7 taken together form a 5-8 membered dinitrogen containing heterocycle optionally substituted with one or more substituent selected from the group consisting of lower alkyl, hydroxy, keto, phenyl, or carboxyl derivatives; and R^8 is selected from the group consisting of alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylthiocarbonyl, or acyloxymethoxycarbonyl; and

R^5 is defined as above

or A is



where R^2 and R^7 taken together form a 5-8 membered dinitrogen containing heterocycle optionally substituted with hydroxy, keto, phenyl, or alkyl; and

R^8 are both selected from the group consisting of alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylthiocarbonyl and acyloxymethoxycarbonyl;

Z^1 is one or more substituent selected from the group consisting of H; alkyl; hydroxy; alkoxy; aryloxy; halogen; haloalkyl; haloalkoxy; nitro; amino; alkylamino; acylamino; dialkylamino; cyano; alkylthio; alkylsulfonyl; carboxyl derivatives; trihaloacetamide; acetamide; aryl; fused aryl; cycloalkyl; thio; monocyclic heterocycles; fused monocyclic heterocycles; and A, wherein A is defined above;

V is selected from the group consisting of $-N-(R^6)-$ wherein R^6 is selected from the group consisting of H; lower alkyl; cycloalkyl; aralkyl; aryl; and monocyclic heterocycles; or R^6 taken together with Y, forms a 4-12 membered mononitrogen containing ring;

Y, Y^3, Z and Z^3 are independently selected from the group consisting of hydrogen; alkyl; aryl; and cycloalkyl; or Y and Z taken together form a cycloalkyl; or Y^3 and Z^3 taken together form a cycloalkyl;

n is an integer 1, 2, or 3;

t is an integer 0, 1, or 2;

p is an integer 0, 1, 2, or 3;

R is $X-R^3$ wherein X is selected from the group consisting of O, S and NR^4, wherein R^3 and R^4 are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; haloalkyl; aryl; arylalkyl; sugars; steroids; polyalkylethers; alkylamido; alkyl N,N-dialkylamido; pivaloyloxymethyl; and in the case

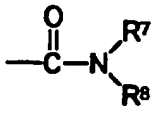
of the free acid, all pharmaceutically acceptable salts thereof;

R^1 is selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; carboxyl derivatives; haloalkyl; cycloalkyl; monocyclic heterocycles; monocyclic heterocycles optionally substituted with alkyl, halogen, haloalkyl, cyano, hydroxy, aryl, fused aryl, nitro, alkoxy, aryloxy, alkylsulfonyl, arylsulfonyl, sulfonamide, thio, alkylthio, carboxyl derivatives, amino, amido;

alkyl optionally substituted with one or more of halo, haloalkyl, hydroxy, alkoxy, aryloxy, thio, alkylthio, alkynyl, alkenyl, alkyl, arylthio, alkylsulfoxide, alkylsulfonyl, arylsulfoxide, arylsulfonyl, cyano, nitro, amino, alkylamino, dialkylamino, alkylsulfonamide, arylsulfonamide, acylamide, carboxyl derivatives, sulfonamide, sulfonic acid, phosphonic acid derivatives, phosphinic acid derivatives, aryl, arylthio, arylsulfoxide, or arylsulfone all optionally substituted on the aryl ring with halo, alkyl, haloalkyl, cyano, nitro, hydroxy, carboxyl derivatives, alkoxy, aryloxy, amino, alkylamino, dialkylamino, amido, aryl, fused aryl, monocyclic heterocycles; and fused monocyclic heterocycles, monocyclic heterocyclicthio, monocyclic heterocyclicsulfoxide, and monocyclic heterocyclic sulfone, which can be optionally substituted with halo, haloalkyl, nitro, hydroxy, alkoxy, fused aryl, or alkyl;

alkylcarbonyl, haloalkylcarbonyl, and arylcarbonyl;

aryl optionally substituted in one or more positions with halo, haloalkyl, alkyl, alkoxy, aryloxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkylthio, thio, hydroxy, cyano, nitro, acyloxy, carboxyl derivatives, carboxyalkoxy; amido, acylamino, amino, alkylamino, dialkylamino, trifluoroalkoxy, trifluoromethylsulfonyl, alkylsulfonyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles and fused monocyclic heterocycles; and

 wherein R^7 and R^8 are as defined above

and provided that taken together with the nitrogen, R^7 and R^8 comprise an amino acid;

and

R^{11} is selected from the group consisting of H, alkyl, aralkyl, alkenyl, alkynyl, haloalkyl or haloalkynyl or R^{11} taken together with Y forms a 4-12 membered mononitrogen containing ring.

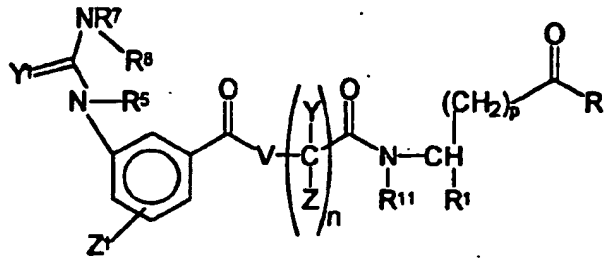
It is another object of the invention to provide pharmaceutical compositions comprising compounds of the Formula I. Such compounds and compositions are useful in selectively inhibiting or antagonizing the $\alpha_v\beta_3$ integrin and therefore in another embodiment the present invention relates to a method of selectively inhibiting or antagonizing the $\alpha_v\beta_3$ integrin. The invention further involves treating or inhibiting pathological conditions associated therewith such as osteoporosis, humoral hypercalcemia of malignancy, Paget's disease, tumor metastasis, solid tumor growth (neoplasia), angiogenesis, including tumor

angiogenesis, retinopathy including diabetic retinopathy, arthritis, including rheumatoid arthritis, periodontal disease, psoriasis, smooth muscle cell migration and restenosis in a mammal in need of such treatment. Additionally, such pharmaceutical agents are useful as antiviral agents, and antimicrobials.

Detailed Description

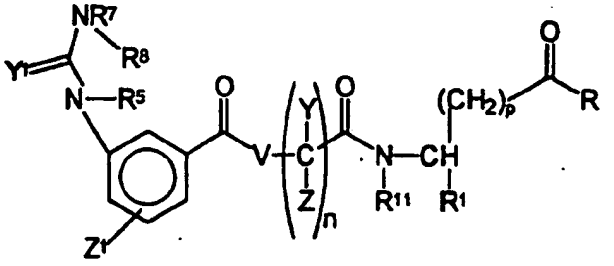
The present invention relates to a class of compounds represented by the Formula I, described above.

A preferred embodiment of the present invention is a compound of the Formula II



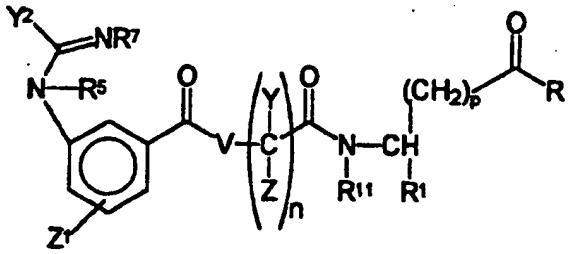
wherein R^5, R^7 and R^8 are independently selected from H, alkyl, aryl, carboxyalkyl, substituted aryl, substituted arylsulfonyl, and arylalkyl or NR^7 and R^8 taken together form a 4-12 membered mononitrogen containing ring optionally substituted and the other variables are as described in Formula I.

Another preferred embodiment of the present invention is a compound of the Formula III



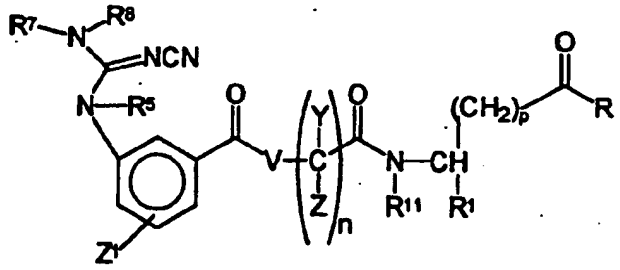
wherein Y^1 is $-NR^2$ and R^2 taken together with R^7 forms an optionally substituted 4-12 membered ring and the other variables are as defined above in Formula I.

Another preferred embodiment of the present invention is a compound of the Formula IV



wherein Y^2 taken together with R^7 forms a 4-12 membered ring and the other variables are as defined above in Formula I.

Another preferred embodiment of the present invention is a compound of the Formula V



wherein the variables are as defined above in Formula I.

The invention further relates to pharmaceutical compositions containing therapeutically effective amounts of the compounds of Formulas I-V.

The invention also relates to a method of selectively inhibiting or antagonizing the $\alpha_v\beta_3$ integrin and more specifically relates to a method of inhibiting bone resorption, periodontal disease, osteoporosis, humoral hypercalcemia of malignancy, Paget's disease, tumor metastasis, solid tumor growth (neoplasia),

angiogenesis, including tumor angiogenesis, retinopathy including diabetic retinopathy, arthritis, including rheumatoid arthritis, smooth muscle cell migration and restenosis by administering a therapeutically effective amount of a compound of the Formula I-V to achieve such inhibition together with a pharmaceutically acceptable carrier.

The following is a list of definitions of various terms used herein:

As used herein, the terms "alkyl" or "lower alkyl" refer to a straight chain or branched chain hydrocarbon radicals having from about 1 to about 10 carbon atoms, and more preferably 1 to about 6 carbon atoms. Examples of such alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, hexyl, isohexyl, and the like.

As used herein the terms "alkenyl" or "lower alkenyl" refer to unsaturated acyclic hydrocarbon radicals containing at least one double bond and 2 to about 6 carbon atoms, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety, relative to groups substituted on the double bond carbons. Examples of such groups are ethenyl, propenyl, butenyl, isobutenyl, pentenyl, hexenyl and the like.

As used herein the terms "alkynyl" or "lower alkynyl" refer to acyclic hydrocarbon radicals containing one or more triple bonds and 2 to about 6 carbon atoms. Examples of such groups are ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

The term "cycloalkyl" as used herein means saturated or partially unsaturated cyclic carbon radicals containing 3 to about 8 carbon atoms and more preferably 4 to about 6 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclopropenyl,

cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, and the like.

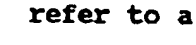
The term "aryl" as used herein denotes aromatic ring systems composed of one or more aromatic rings. Preferred aryl groups are those consisting of one, two or three aromatic rings. The term embraces aromatic radicals such as phenyl, pyridyl, naphthyl, thiophene, furan, biphenyl and the like.

As used herein, the term "cyano" is represented by a radical of the formula  .

The terms "hydroxy" and "hydroxyl" as used herein are synonymous and are represented by a radical of the formula  .

The term "lower alkylene" or "alkylene" as used herein refers to divalent linear or branched saturated hydrocarbon radicals of 1 to about 6 carbon atoms.

As used herein the term "alkoxy" refers to straight or branched chain oxy containing radicals of the formula $-OR^{20}$, wherein R^{20} is an alkyl group as defined above. Examples of alkoxy groups encompassed include methoxy, ethoxy, n-propoxy, n-butoxy, isopropoxy, isobutoxy, sec-butoxy, t-butoxy and the like.

As used herein the terms "arylalkyl" or "aralkyl" refer to a radical of the formula  wherein R^{21} is aryl as defined above and R^{22} is an alkylene as defined above. Examples of aralkyl groups include benzyl, pyridylmethyl, naphthylpropyl, phenethyl and the like.

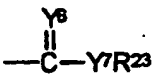
As used herein the term "nitro" is represented by a radical of the formula .

As used herein the term "halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

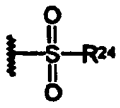
As used herein the term "haloalkyl" refers to alkyl groups as defined above substituted with one or more of the same or different halo groups at one or more carbon atom. Examples of haloalkyl groups include trifluoromethyl, dichloroethyl, fluoropropyl and the like.

As used herein the term "carboxyl" or "carboxy" refers to a radical of the formula -COOH.

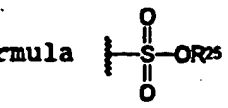
As used herein the term "carboxyl ester" refers to a radical of the formula $-COOR^{23}$ wherein R^{23} is selected from the group consisting of H, alkyl, aralkyl or aryl as defined above.

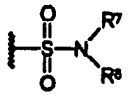
As used herein the term "carboxyl derivative" refers to a radical of the formula  wherein Y^6 and Y^7 are independently selected from the group consisting of O, N or S and R^{23} is selected from the group consisting of H, alkyl, aralkyl or aryl as defined above.

As used herein the term "amino" is represented by a radical of the formula $-NH_2$.

As used herein the term "alkylsulfonyl" or "alkylsulfone" refers to a radical of the formula  wherein R^{24} is alkyl as defined above.

As used herein the term "alkylthio" refers to a radical of the formula $-SR^{24}$ wherein R^{24} is alkyl as defined above.

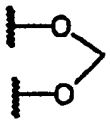
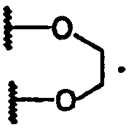
As used herein the term "sulfonic acid" refers to a radical of the formula  wherein R^{25} is H, alkyl or aryl as defined above.

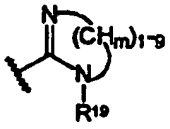
As used herein the term "sulfonamide" refers to a radical of the formula  wherein R^7 and R^8 are as defined above.

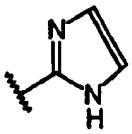
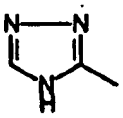
As used herein the term "fused aryl" refers to an aromatic ring such as the aryl groups defined above fused to one or more phenyl rings. Embraced by the term "fused aryl" is the radical naphthyl.

As used herein the terms "monocyclic heterocycle" or "monocyclic heterocyclic" refer to a monocyclic ring containing from 4 to about 12 atoms, and more preferably from 5 to about 10 atoms, wherein 1 to 3 of the atoms are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur with the understanding that if two or more different heteroatoms are present at least one of the heteroatoms must be nitrogen. Representative of such monocyclic heterocycles are imidazole, furan, pyridine, oxazole, pyran, triazole, thiophene, pyrazole, thiazole, thiadiazole, and the like.

As used herein the term "fused monocyclic heterocycle" refers to a monocyclic heterocycle as defined above with a benzene fused thereto. Examples of such fused monocyclic heterocycles include benzofuran, benzopyran, benzodioxole, benzothiazole, benzothiophene, benzimidazole and the like.

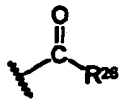
As used herein the term "methylenedioxy" refers to the radical  and the term "ethylenedioxy" refers to the radical  .

As used herein the term "4-12 membered dinitrogen containing heterocycle refers to a radical of the formula  wherein m is 1 or 2 and R^{19} is H, alkyl, aryl, or aralkyl and more preferably refers to 4-9 membered ring and includes rings such as imidazoline.

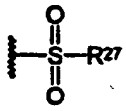
As used herein the term "5-membered optionally substituted heteroaromatic ring" includes for example a radical of the formula  or  and

"5-membered heteroaromatic ring fused with a phenyl" refers to such a "5-membered heteroaromatic ring" with a phenyl fused thereto. Representative of such 5-membered heteroaromatic rings fused with a phenyl is benzimidazole.

As used herein the term "bicycloalkyl" refers to a bicyclic hydrocarbon radical containing 6 to about 12 carbon atoms which is saturated or partially unsaturated.

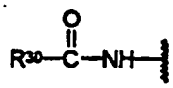
As used herein the term "acyl" refers to a radical of the formula  wherein R^{26} is alkyl, alkenyl, alkynyl, aryl or aralkyl and optionally substituted thereon as defined above. Encompassed by such radical are the groups acetyl, benzoyl and the like.

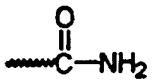
As used herein the term "thio" refers to a radical of the formula  .

As used herein the term "sulfonyl" refers to a radical of the formula  wherein R^{27} is alkyl, aryl or aralkyl as defined above.

As used herein the term "haloalkylthio" refers to a radical of the formula $-S-R^{28}$ wherein R^{28} is haloalkyl as defined above.

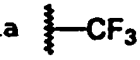
As used herein the term "aryloxy" refers to a radical of the formula  wherein R^{29} is aryl as defined above.

As used herein the term "acylamino" refers to a radical of the formula  wherein R^{30} is alkyl, aralkyl or aryl as defined above.

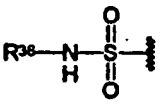
As used herein the term "amido" refers to a radical of the formula  .

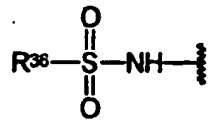
As used herein the term "alkylamino" refers to a radical of the formula $-NHR^{32}$ wherein R^{32} is alkyl as defined above.

As used herein the term "dialkylamino" refers to a radical of the formula $-NR^{33}R^{34}$ wherein R^{33} and R^{34} are the same or different alkyl groups as defined above.

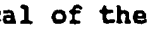
As used herein the term "trifluoromethyl" refers to a radical of the formula  .

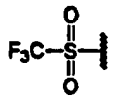
As used herein the term "trifluoroalkoxy" refers to a radical of the formula  wherein R^{35} is a bond or an alkylene as defined above.

As used herein the term "alkylaminosulfonyl" refers to a radical of the formula  wherein R^{36} is alkyl as defined above.

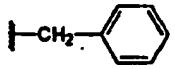
As used herein the term "alkylsulfonylamino" refers to a radical of the formula 

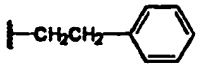
wherein R^{36} is alkyl as defined above.

As used herein the term "trifluoromethylthio" refers to a radical of the formula  .

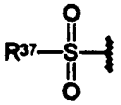
As used herein the term "trifluoromethylsulfonyl" refers to a radical of the formula  .

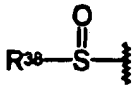
As used herein the term "4-12 membered mono-nitrogen containing monocyclic or bicyclic ring" refers to a saturated or partially unsaturated monocyclic or bicyclic ring of 4-12 atoms and more preferably a ring of 4-9 atoms wherein one atom is nitrogen. Such rings may optionally contain additional heteroatoms selected from nitrogen, oxygen or sulfur. Included within this group are morpholine, piperidine, piperazine, thiomorpholine, pyrrolidine, proline, azacycloheptene and the like.

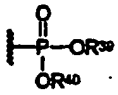
As used herein the term "benzyl" refers to the radical  .

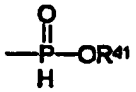
As used herein the term "phenethyl" refers to the radical  .

As used herein the term "4-12 membered mono-nitrogen containing monosulfur or monooxygen containing heterocyclic ring" refers to a ring consisting of 4 to 12 atoms and more preferably 4 to 9 atoms wherein at least one atom is a nitrogen and at least one atom is oxygen or sulfur. Encompassed within this definition are rings such as thiazoline and the like.

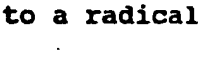
As used herein the term "arylsulfonyl" or "arylsulfone" refers to a radical of the formula  wherein R^{37} is aryl as defined above.

As used herein the terms "alkylsulfoxide" or "arylsulfoxide" refer to radicals of the formula  wherein R^{38} is, respectively, alkyl or aryl as defined above.

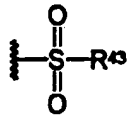
As used herein the term "phosphonic acid derivative" refers to a radical of the formula  wherein R^{39} and R^{40} are the same or different H, alkyl, aryl or aralkyl.

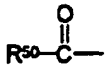
As used herein the term "phosphinic acid derivatives" refers to a radical of the formula  wherein R^{41} is H, alkyl, aryl or aralkyl as defined above.

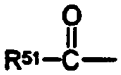
As used herein the term "arylthio" refers to a radical of the formula wherein R^{42} is aryl as defined above.

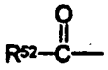
As used herein the term "monocyclic heterocycle thio" refers to a radical of the formula  wherein R^{43} is a monocyclic heterocycle radical as defined above.

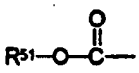
As used herein the terms "monocyclic heterocycle sulfoxide" and "monocyclic heterocycle sulfone" refer, respectively, to radicals of the formula  and

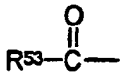
 wherein R^{43} is a monocyclic heterocycle radical as defined above.

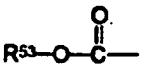
As used herein the term "alkylcarbonyl" refers to a radical of the formula  wherein R^{50} is alkyl as defined above.

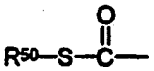
As used herein the term "arylcarbonyl" refers to a radical of the formula  wherein R^{51} is aryl as defined above.

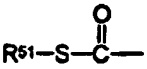
As used herein the term "alkoxycarbonyl" refers to a radical of the formula  wherein R^{52} is alkoxy as defined above.

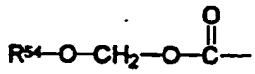
As used herein the term "aryloxycarbonyl" refers to a radical of the formula  wherein R^{51} is aryl as defined above.

As used herein the term "haloalkylcarbonyl" refers to a radical of the formula  wherein R^{53} is haloalkyl as defined above.

As used herein the term "haloalkoxycarbonyl" refers to a radical of the formula  wherein R^{53} is haloalkyl as defined above.

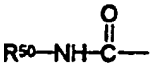
As used herein the term "alkylthiocarbonyl" refers to a radical of the formula  wherein R^{50} is alkyl as defined above.

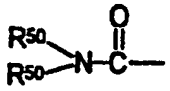
As used herein the term "arylthiocarbonyl" refers to a radical of the formula  wherein R^{51} is aryl as defined above.

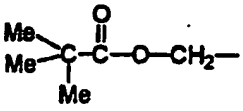
As used herein the term "acyloxymethoxycarbonyl" refers to a radical of the formula  wherein R^{54} is acyl as defined above.

As used herein the term "arylamino" refers to a radical of the formula R^{51}-NH- wherein R^{51} is aryl as defined above.

As used herein the term "polyalkylether" refers to commonly used glycols such as triethyleneglycol, tetraethylene glycol, polyethylene glycol and the like.

As used herein the term "alkylamido" refers to a radical of the formula  wherein R^{50} is alkyl as defined above.

As used herein the term "N,N-dialkylamido" refers to a radical of the formula  wherein R^{50} is the same or different alkyl group as defined above.

As used herein the term "pivaloyloxymethyl" refers to a radical of the formula  .

As used herein the term "acyloxy" refers to a radical of the formula R^{55}-O- wherein R^{55} is acyl as defined above.

The term "composition" as used herein means a product which results from the mixing or combining of more than one element or ingredient.

The term "pharmaceutically acceptable carrier", as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician.

The following is a list of abbreviations and the corresponding meanings as used interchangeably herein:

^{1}H-NMR = proton nuclear magnetic resonance
AcOH = acetic acid
BH_3-THF = borane-tetrahydrofuran complex
Bn = benzyl
BOC = tert-butoxycarbonyl
ButLi = butyl lithium
Cat. = catalytic amount
CH_2Cl_2 = dichloromethane

CH_3CN = acetonitrile
CH_3I = iodomethane
CHN analysis = carbon/hydrogen/nitrogen elemental analysis
CHNCl analysis = carbon/hydrogen/nitrogen/chlorine elemental analysis
CHNS analysis = carbon/hydrogen/nitrogen/sulfur elemental analysis
DCC = 1,3-dicyclohexylcarbodiimide
DIBAL = diisobutylaluminum hydride
DIEA = diisopropylethylamine
DMA = N,N-dimethylacetamide
DMAP = 4-(N,N-dimethylamino)pyridine
DMF = N,N-dimethylformamide
DSC = disuccinyl carbonate
EDCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et = ethyl
Et_2O = diethyl ether
Et_3N = triethylamine
EtOAc = ethyl acetate
EtOH = ethanol
FAB MS = fast atom bombardment mass spectroscopy
g = gram(s)
GIHA = *meta*-guanidinohippuric acid
GIHA HCl = meta-guanidinohippuric acid hydrochloride
HPLC = high performance liquid chromatography
IBCF = isobutylchloroformate
i-Pr = iso propyl
i-Prop = iso propyl
K_2CO_3 = potassium carbonate
KOH = potassium hydroxide
KSCN = potassium thiocyanate
LiOH = lithium hydroxide
MCPBA = m-chloroperoxybenzoic acid or m-chloroperbenzoic acid
Me = methyl
MeOH = methanol
MesCl = methanesulfonylchloride
mg = milligram
$MgSO_4$ = magnesium sulfate
ml = milliliter
mL = milliliter
MS = mass spectroscopy
N_2 = nitrogen
$NaCNBH_3$ = sodium cyanoborohydride
NaH = sodium hydride
$NaHCO_3$ = sodium bicarbonate
NaOH = sodium hydroxide
Na_2PO_4 = sodium phosphate
Na_2SO_4 = sodium sulfate
NEt_3 = triethylamine
NH_4HCO_3 = ammonium bicarbonate
$NH_4^+HCO_2^-$ = ammonium formate

NMM = N-methylmorpholine
NMR = nuclear magnetic resonance
RPHPLC = reverse phase high performance liquid chromatography
RT = room temperature
Pd/C = palladium on carbon
Ph = phenyl
Pt/C = platinum on carbon
t-BOC = tert-butoxycarbonyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TMEDA = trimethylethylenediamine
TMS = trimethylsilyl
Δ = heating the reaction mixture

The compounds as shown in Formulas I-V can exist in various isomeric forms and all such isomeric forms are meant to be included. Tautomeric forms are also included as well as pharmaceutically acceptable salts of such isomers and tautomers.

In the structures and formulas herein, a bond drawn across a bond of a ring can be to any available atom on the ring.

The term "pharmaceutically acceptable salt" refers to a salt prepared by contacting a compound of Formula I with an acid whose anion is generally considered suitable for human consumption. Examples of pharmacologically acceptable salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, tartrate salts and the like. All of the pharmacologically acceptable salts may be prepared by conventional means. (See Berge et al., J Pharm. Sci., 66(1), 1-19 (1977) for additional examples of pharmaceutically acceptable salts.)

For the selective inhibition or antagonism of $\alpha_v\beta_3$ integrins, compounds of the present invention may be administered orally, parenterally, or by inhalation spray, or topically in unit dosage formulations containing conventional pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes, for example, subcutaneous,

intravenous, intramuscular, intrasternal, infusion techniques or intraperitonally.

The compounds of the present invention are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds required to prevent or arrest the progress of or to treat the medical condition are readily ascertained by one of ordinary skill in the art using preclinical and clinical approaches familiar to the medicinal arts.

Accordingly, the present invention provides a method of treating conditions mediated by selectively inhibiting or antagonizing the $\alpha_v\beta_3$ cell surface receptor which method comprises administering a therapeutically effective amount of a compound selected from the class of compounds depicted in Formulas I-V, wherein one or more compounds of the Formulas I-V is administered in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and if desired other active ingredients. More specifically, the present invention provides a method for inhibition of the $\alpha_v\beta_3$ cell surface receptor. Most preferably the present invention provides a method for inhibiting bone resorption, treating osteoporosis, inhibiting humoral hypercalcemia of malignancy, treating Paget's disease, inhibiting tumor metastasis, inhibiting neoplasia (solid tumor growth), inhibiting angiogenesis including tumor angiogenesis, treating diabetic retinopathy, inhibiting arthritis, psoriasis and periodontal disease, and inhibiting smooth muscle cell migration including restenosis.

Based upon standard laboratory experimental techniques and procedures well known and appreciated by those skilled in the art, as well as comparisons with

compounds of known usefulness, the compounds of Formula I can be used in the treatment of patients suffering from the above pathological conditions. One skilled in the art will recognize that selection of the most appropriate compound of the invention is within the ability of one with ordinary skill in the art and will depend on a variety of factors including assessment of results obtained in standard assay and animal models.

Treatment of a patient afflicted with one of the pathological conditions comprises administering to such a patient an amount of compound of the Formula I which is therapeutically effective in controlling the condition or in prolonging the survivability of the patient beyond that expected in the absence of such treatment. As used herein, the term "inhibition" of the condition refers to slowing, interrupting, arresting or stopping the condition and does not necessarily indicate a total elimination of the condition. It is believed that prolonging the survivability of a patient, beyond being a significant advantageous effect in and of itself, also indicates that the condition is beneficially controlled to some extent.

As stated previously, the compounds of the invention can be used in a variety of biological, prophylactic or therapeutic areas. It is contemplated that these compounds are useful in prevention or treatment of any disease state or condition wherein the $\alpha_v\beta_3$ integrin plays a role.

The dosage regimen for the compounds and/or compositions containing the compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. Dosage levels of the order from about 0.01 mg to about 100 mg per kilogram

of body weight per day are useful in the treatment of the above-indicated conditions.

The active ingredient administered by injection is formulated as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose would typically be about 0.01 to 10 mg/kg body weight injected per day in multiple doses depending on the factors listed above.

For administration to a mammal in need of such treatment, the compounds in a therapeutically effective amount are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

The pharmaceutical compositions useful in the present invention may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

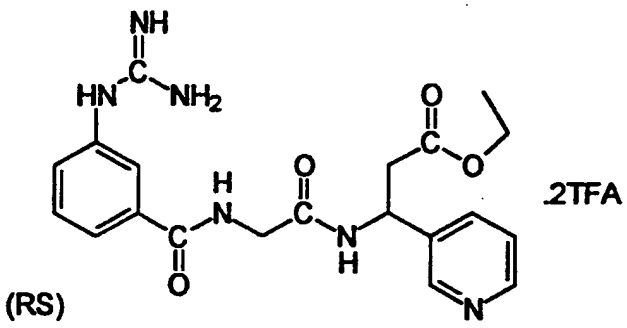
The general synthetic sequences for preparing the compounds useful in the present invention are outlined in Schemes I-XXI. Both an explanation of, and the actual procedures for, the various aspects of the present invention are described where appropriate. The

following Schemes and Examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the Schemes and Examples can be used to synthesize the compounds of the present invention.

Unless otherwise indicated all starting materials and equipment employed were commercially available.

Example 1

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

To 3-pyridine carboxaldehyde (300 ml) in 2-propanol (3 liters) was added ammonium acetate (297 g) followed by malonic acid (398 g). The reaction mixture was stirred at reflux for 5 hours. The precipitate was filtered while hot and washed with hot isopropanol (2 liters). The resulting white solid was then dried to yield DL-3-amino-3-(3-pyridyl)propionic acid (220 g) as a white solid.

NMR and MS were consistent with the desired product.

Step B

DL-3-amino-3-(3-pyridyl)propionic acid (220 g) from Step A was slurried in absolute EtOH (3.6 liters). HCl gas (one lecture bottle - ½ lb) was bubbled into the reaction while stirring over 40 minutes (slow exotherm to 61°C). The slurry was then heated at reflux for 4 hours (a solution forms after 1 to 1.5 hours). The reaction mixture was cooled to 5°C in an ice bath. After stirring at 5°C for 1.5 hours, the resulting white precipitate was filtered and washed thoroughly with ether. After drying under vacuum at 50°C, the yield of ethyl DL-3-amino-3-(3-

pyridyl)propionate dihydrochloride was 331.3 g as a white solid.

NMR and MS were consistent with the desired product.

Step C

To ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride (220.6 g, 0.83 mole) from Step B in anhydrous THF (2 liters) and triethylamine (167.2 g, 1.65 moles), N-t-BOC-glycine N-hydroxysuccinimide ester (225 g, 0.826 moles)(Sigma) was added in several portions at 5-10°C (no exotherm). The reaction mixture was stirred overnight at room temperature. The resulting precipitate was filtered and washed with THF. The solvent from the filtrate was then removed under vacuum. The residue was taken up in ethyl acetate (2.3 liters). The ethyl acetate layer was washed with saturated sodium bicarbonate (2 x 900 ml) and H_2O (3 x 900 ml), dried over $MgSO_4$ and removed under vacuum. The residue was slurried overnight in 10% ethyl acetate/hexane (2.5 liters). The precipitate was filtered, washed with 10% ethyl acetate/hexane (1 liter), then hexane, then dried to yield ethyl β-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]acetyl]amino]-pyridine-3-propanoate (233 g) as a white solid.

NMR and MS were consistent with the desired structure.

Step D

Ethyl β-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-acetyl]amino]pyridine-3-propanoate (from Step C) (232 g, 0.66 mole) was dissolved in warm dioxane (1 liter). After cooling to room temperature, 4M HCl in dioxane (1.6 liters) (Aldrich) was slowly added. A white precipitate formed after several minutes and then turned to a thick goo. After 2 hours, the solvent was decanted off. The goo was slurried in ether and the

ether decanted off until a white solid resulted. This was dried under vacuum to yield ethyl β-[(2-aminoacetyl)amino]pyridine-3-propanoate, bis hydrochloride salt (224.2 g) as a white hygroscopic solid.

NMR and MS were consistent with the desired structure.

Step E

To 3,5-dimethylpyrazole-1-carboxamidine nitrate (6 g, 0.03 mole) (Aldrich) and diisopropylamine (3.8 g, 0.03 mole) in dioxane (20 ml) and H_2O (10 ml) was added 3-aminobenzoic acid (2.7 g, 0.02 mole). The reaction was stirred at reflux for 2.5 hours then overnight at room temperature. The resulting precipitate was filtered, washed with dioxane/H_2O and dried. The precipitate was then slurried in H_2O and acidified with concentrated HCl until a solution formed. The solvent was removed under vacuum and the residue was slurried twice in ether (ether decanted off). The product was dried under vacuum to yield 3-guanidinobenzoic acid hydrochloride (1.77 g) as a white solid. MS and NMR were consistent with the desired structure.

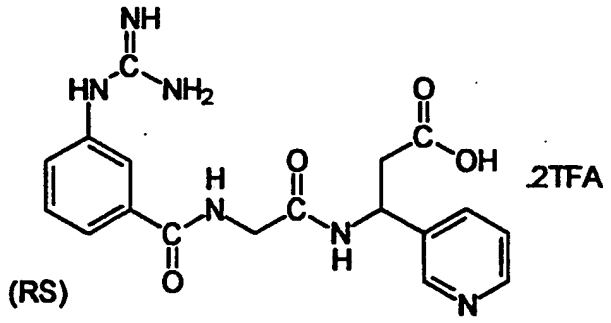
Step F

To the product from Step E (0.49 g, 0.0023 mole) and N-methylmorpholine (0.23 g, 0.0023 mole) in anhydrous DMF (8 ml) was added isobutylchloroformate (0.31 g, 0.0023 mole) at ice bath temperature. After stirring for 5 minutes at ice bath temperature, a slurry of the product from Step D (0.73 g, 0.0023 mole) and N-methylmorpholine (0.46 g, 0.0045 mole) in anhydrous DMF (8 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath and the product was isolated by RPHPLC to yield (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-

amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt (800 mg) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

Example 2

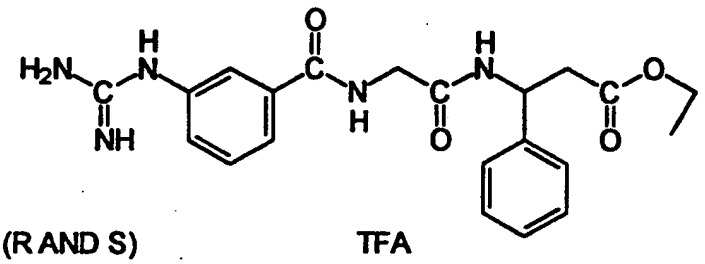
Preparation of (±)β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product from Example 1 (700 mg, 0.001 mole), in H_2O (20 ml) was added LiOH (160 mg, 0.0038 mole). The reaction mixture was stirred for 1 hour at room temperature. After lowering the pH to ≈5 with TFA, the product was isolated by RPHPLC to yield (±)β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (640 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 3

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoate, trifluoroacetate salt



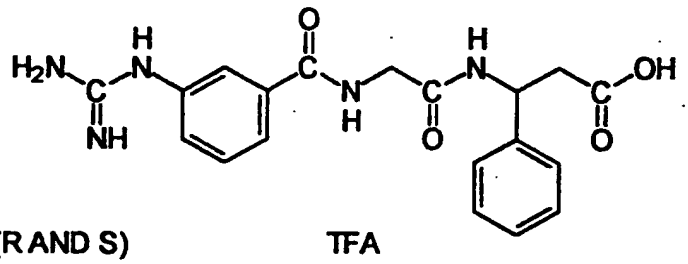
(R AND S) TFA

The above compound was prepared according to the methodology of Example 1, substituting an equivalent amount of benzaldehyde for 3-pyridinecarboxaldehyde in Step A.

NMR and MS were consistent with the desired structure.

Example 4

Preparation of (±)β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]benzene-propanoic acid, trifluoroacetate salt

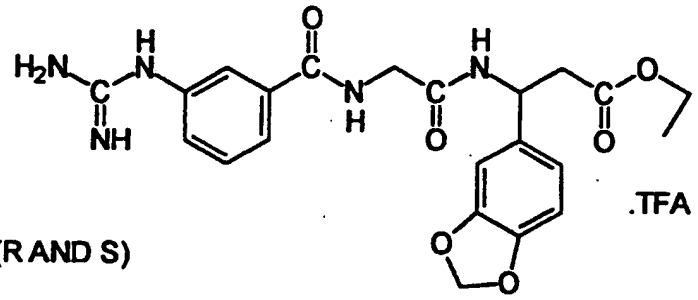


(R AND S) TFA

To the product of Example 3 (0.37 g, 0.0007 mole) in H_2O (10 ml) was added LiOH (80 mg, 0.002 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ≈3 with TFA and the product was isolated by RPHPLC to yield β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt (280 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 5

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoate, trifluoroacetate salt

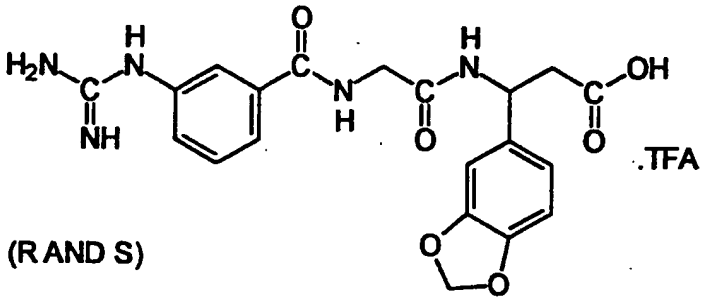


The above compound was prepared according to the methodology of Example 1, substituting the equivalent amount of piperonal (Aldrich) for 3-pyridinecarboxaldehyde in Step A.

MS and NMR were consistent with the desired structure.

Example 6

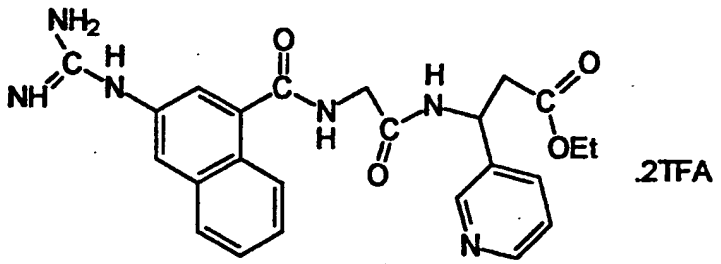
Preparation of (±)β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid, trifluoroacetate salt



To the product of Example 5 (0.35 g, 0.0006 mole) in H_2O (40 ml) and CH_3CN (5 ml) was added LiOH (70 mg, 0.0017 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ≃4.5 with TFA and the product was isolated by RPHPLC to yield (±)β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid, trifluoroacetate salt (280 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 7

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]naphthalen-1-yl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoate, bis(trifluoroacetate)salt



(RACEMIC)

Step A

To methyl 3-nitro-1-naphthoate (2.5 g, 0.011 mole)(Aldrich) in MeOH/H_2O (40 ml)(1:1) was added LiOH (1.8 g, 4 equivalents). The solution was stirred overnight at room temperature. The solvent was removed under a stream of N_2. The residue was dissolved in H_2O and the solution acidified with concentrated HCl. The resulting precipitate was filtered, washed with H_2O and dried to yield 3-nitro-1-naphthoic acid (2.18 g) as a white solid.

Step B

3-Nitro-1-naphthoic acid (1.77 g, 0.008 mole) was dissolved in a minimum of warm MeOH. 10% Pd/C (300 mg) was added and the reaction shaken on a Parr shaker under 50 psi H_2 for 5 hours. The catalyst was filtered through celite and the solvent was removed under vacuum. The residue was dried to yield 3-amino-1-naphthoic acid (1.43 g) as a pink colored solid.

Step C

To 3,5-dimethylpyrazole-1-carboxamidine nitrate (1.6 g, 0.008 mole)(Aldrich) and diisopropylethylamine (1.02 g, 0.008 mole) in dioxane (5 ml) and H_2O (2.5 ml) was added 3-amino-1-naphthoic acid (1 g, 0.0053 mole). The reaction mixture was stirred at reflux overnight. The reaction was cooled to room temperature and the precipitate was filtered, washed with dioxane/H_2O then dried. The precipitate was then slurried in H_2O and acidified with concentrated HCl. The solvent was removed under vacuum on a 70°C water bath. The residue was slurried in ether 3 x (ether decanted off), then dried under vacuum to yield 3-guanidino-1-naphthoic acid hydrochloride (460 mg) as a white solid.

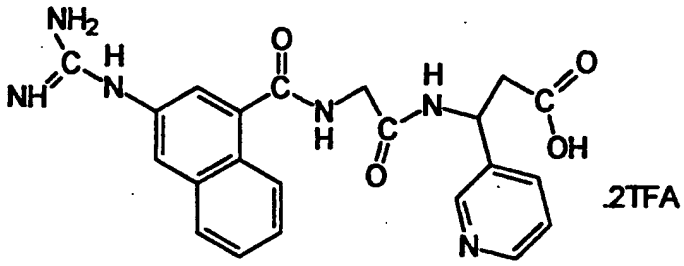
Step D

To 3-guanidino-1-naphthoic acid hydrochloride (400 mg, 0.0015 mole) and N-methylmorpholine (150 mg) in anhydrous DMF (8 ml) was added isobutylchloroformate (210 mg) at ice bath temperature. After stirring at ice bath temperature for 5 minutes, a slurry of the product from Example 1, Step D (490 mg, 0.0015 mole), N-methylmorpholine (300 mg) and anhydrous DMF (6 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath. The product was isolated by RPHPLC to yield (±)ethyl β-[[2-[[[1-[(aminoiminomethyl)amino]naphthalen-3-yl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate)salt (410 mg) as a white solid.

NMR and MS were consistent with the desired structure.

Example 8

Preparation of (±)β-[[2-[[[3-[(aminoiminomethyl)-amino]naphthalen-1-yl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt

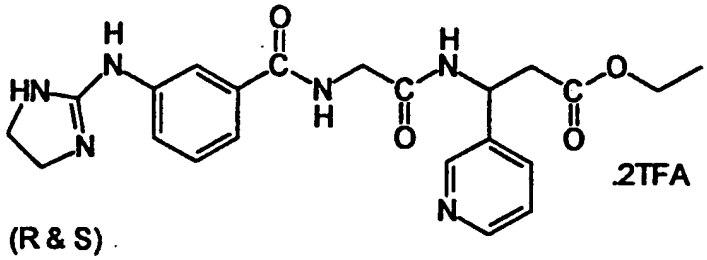


(RACEMIC)

To the product of Example 7, Step D (280 mg, 0.0004 mole) in H_2O (15 ml) and CH_3CN (2 ml) was added (70 mg, 0.0016 mole) LiOH. The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield (±)β-[[2-[[[1-[(aminoiminomethyl)-amino]naphthalen-3-yl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (240 mg) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

Example 9

Preparation of (±)ethyl β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



(R & S)

Step A

To 2-methylthio-2-imidazoline hydroiodide (14.6 g, 0.06 mole)(Aldrich) and diisopropylethylamine (7.6 g, 0.06 mole) in dioxane (40 ml) and H_2O (20 ml) was added 3-aminobenzoic acid (5.4 g, 0.04 mole). The reaction was stirred overnight at reflux. The solution was cooled in an ice bath and the resulting precipitate was filtered and washed with dioxane. The crude product was purified by RPHPLC to yield 3-(2-aminoimidazoline)-benzoic acid (800 mg).

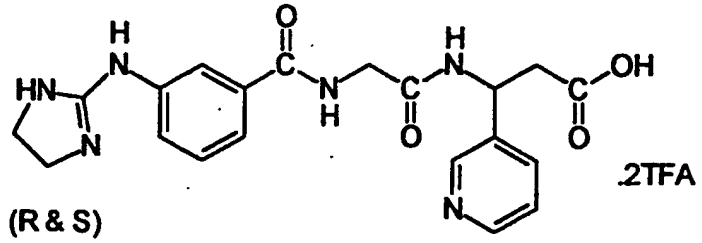
Step B

To the product from Step A (400 mg, 0.00125 mole) and N-methylmorpholine (130 mg, 0.00125 mole) in anhydrous DMF (8 ml) was added isobutylchloroformate (170 mg, 0.00125 mole). After stirring at ice bath temperature for 5 minutes, the product from Example 1, Step D (410 mg, 0.00125 mole) and N-methylmorpholine (250 mg, 0.0025 mole) in anhydrous DMF (6 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 79°C water bath and the product was isolated by RPHPLC to yield (±)ethyl β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoate,

bis(trifluoroacetate) salt (600 mg) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

Example 10

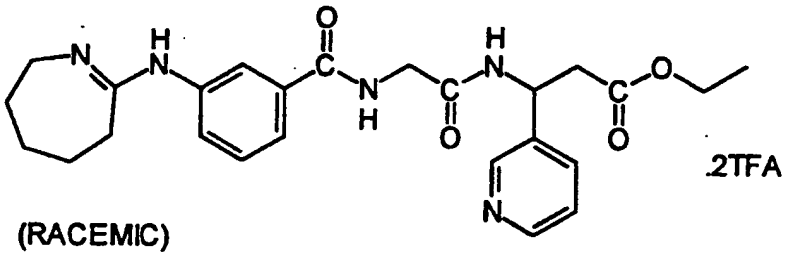
Preparation of (±)β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 9, Step B (450 mg, 0.00068 mole) in H_2O (20 ml) was added LiOH (110 mg, 0.0027 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield (±)β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt (250 mg) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

Example 11

Preparation of (±) ethyl β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



(RACEMIC)

Step A

To 1-aza-2-methoxy-1-cycloheptene (3.67 g, 0.0288 mole)(Aldrich) in absolute ethanol (20 ml) was added 3-aminobenzoic acid hydrochloride (5 g, 0.0288 mole). A solution quickly formed. The reaction mixture was stirred overnight at room temperature. The resulting precipitate was filtered, washed with ether and dried under vacuum to yield 3-(1-aza-2-amino-1-cycloheptene)-benzoic acid (4.9 g).

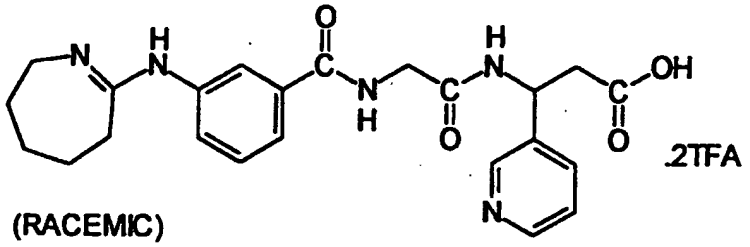
Step B

To the product from Step A (0.5 g, 0.0019 mole) and N-methylmorpholine (0.19 g, 0.0019 mole) in anhydrous DMF (8 ml) was added isobutylchloroformate (0.25 g, 0.0019 mole) at ice bath temperature. After stirring at ice bath temperature for 5 minutes, a slurry of the product from Example 1, Step D (0.6 g, 0.0019 mole) and N-methylmorpholine (0.38 g, 0.0037 mole) in anhydrous DMF (7 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath and the product was isolated by RPHPLC

to yield the title compound (490 mg). NMR and MS were consistent with the desired structure.

Example 12

Preparation of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt

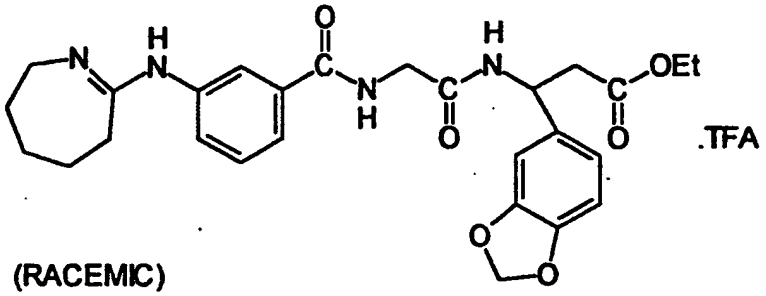


(RACEMIC)

To the product of Example 11, Step B (400 mg, 0.00058 mole) in H_2O (20 ml) was added LiOH (80 mg, 0.0019 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to 4.5 with TFA and the product was isolated by RPHPLC to yield 320 mg of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt as a white solid. MS and NMR are consistent with the desired structure.

Example 13

Preparation of (±)ethyl β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]-1,3-benzodioxole-5-propanoate, TFA salt



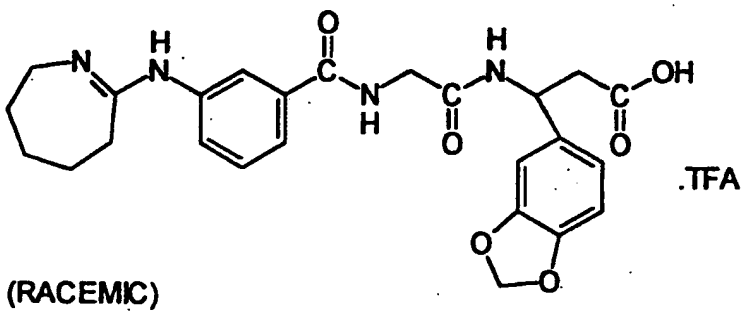
(RACEMIC)

The above compound was prepared according to the methodology of Example 11, substituting the equivalent amount of piperonal (Aldrich) for 3-pyridine-carboxaldehyde in Example 1, Step A, in Example 11, Step B.

MS and NMR were consistent with the desired structure.

Example 14

Preparation of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid, TFA salt

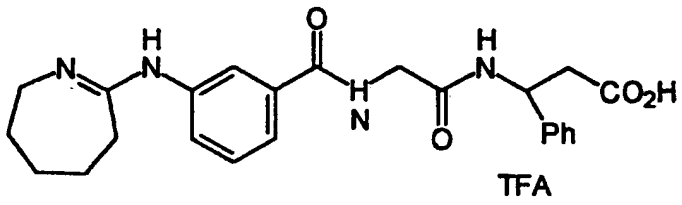


(RACEMIC)

To the product of Example 13 (0.46 g, 0.00091 mole) in H_2O (10 ml) and dioxane (7.5 ml) was added LiOH (80 mg, 0.0018 mole). The reaction was stirred at room temperature for 2 hours. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid (440 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 15

Preparation of (±)β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid, trifluoroacetate salt



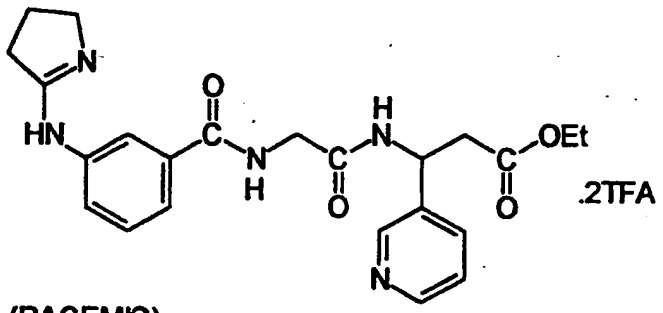
TFA

The above compound was prepared according to the methodology of Example 12, substituting the equivalent amount of benzaldehyde for 3-pyridinecarboxaldehyde in Example 1, Step A, and further used in Example 1, Step D as described in Example 11, Step B.

MS and NMR were consistent with the desired structure.

Example 16

Preparation of (±) ethyl β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoate, bis(trifluoroacetate) salt



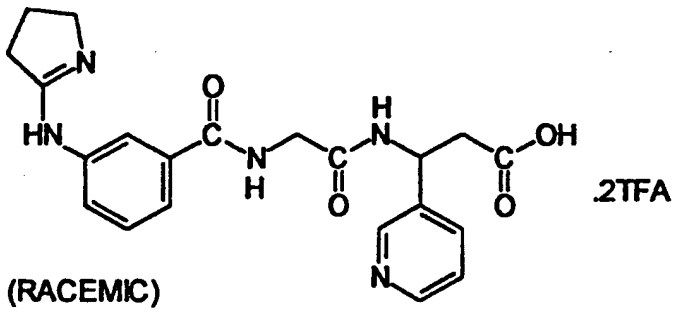
(RACEMIC)

The above compound was prepared according to the methodology of Example 11, substituting 1-aza-2-methoxy-1-cyclopentene* for 1-aza-2-methoxy-1-cycloheptene in Step A. MS and NMR were consistent with the desired structure.

* 1-aza-2-methoxy-1-cyclopentene was made as follows: To 2-pyrrolidinone (2.7 g, 0.033 mole) in CH_2Cl_2 (100 ml) was added trimethyloxonium tetrafluoroborate (10 g)(Aldrich). The reaction was stirred at room temperature for 2 days. Saturated $NaHCO_3$ was added and after shaking in a separatory funnel, the CH_2Cl_2 was separated and distilled off. 1 g of desired product was isolated by further distillation at atmospheric pressure collecting the portion boiling at ≈120°C.

Example 17

Preparation of β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt

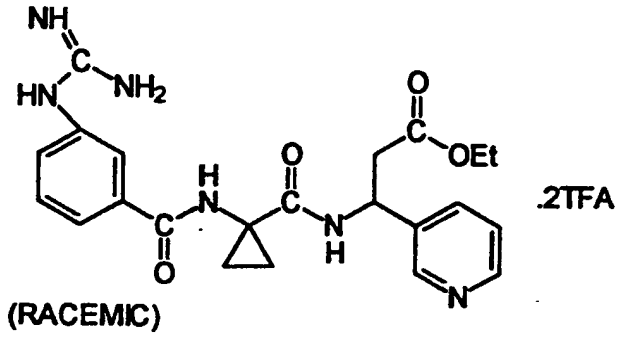


(RACEMIC)

To the product of Example 16 (380 mg, 0.00057 mole) in H_2O (15 ml) was added LiOH (100 mg, 0.002 mole). The reaction was stirred at room temperature for 2 hours. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (150 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 18

Preparation of (±) ethyl β-[[1-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]-1-cyclopropyl]carbonyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



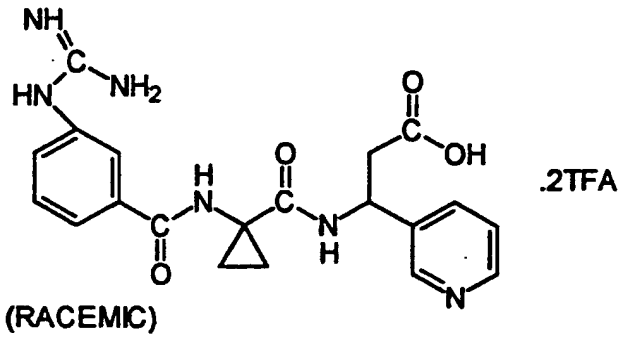
(RACEMIC)

The above compound was prepared according to the methodology of Example 1, substituting an equivalent amount of 1-(N-t-Boc-amino)cyclopropane-N-hydroxysuccinimide carboxylate (Sigma) for N-t-BOC-glycine N-hydroxysuccinimide ester in Example 1, Step C.

MS and NMR were consistent with the desired structure.

Example 19

Preparation of β-[[1-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]cycloprop-1-yl]carbonyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt

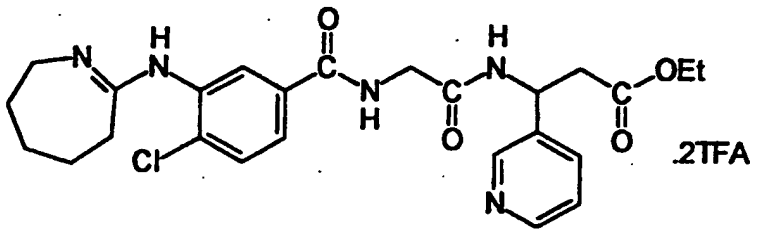


(RACEMIC)

To the product of Example 18 (220 mg, 0.00033 mole) in H_2O (15 ml) was added LiOH (60 mg, 0.0013 mole). The reaction was stirred at room temperature for 1.5 hours. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield β-[[1-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]-cycloprop-1-yl]carbonyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (170 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 20

Preparation of (±)ethyl β-[[2-[[[4-chloro-3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoate, bis TFA salt

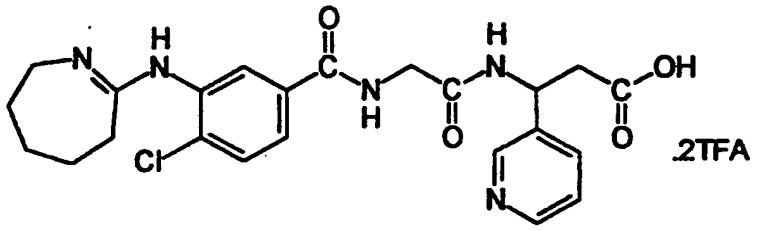


(RACEMIC)

The above compound was prepared according to the methodology of Example 11, substituting an equivalent amount of 3-amino-4-chloro-benzoic acid hydrochloride (Aldrich) for 3-amino-benzoic acid hydrochloride in Example 11, Step A. MS and NMR were consistent with the desired structure.

Example 21

Preparation of (±) β-[[2-[[[4-chloro-3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, bis TFA Salt

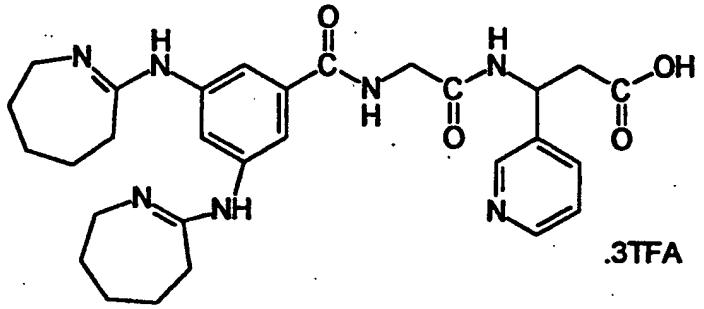


(RACEMIC)

To the product of Example 20 (150 mg, 0.0002 mole) in H_2O (15 ml) was added LiOH (40 mg, 0.0008 mole). The reaction was stirred at room temperature for 1 hour. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[4-chloro-3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid (100 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 22

Preparation of (±) β-[[2-[[[3,5-bis[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, tris(trifluoroacetate) salt

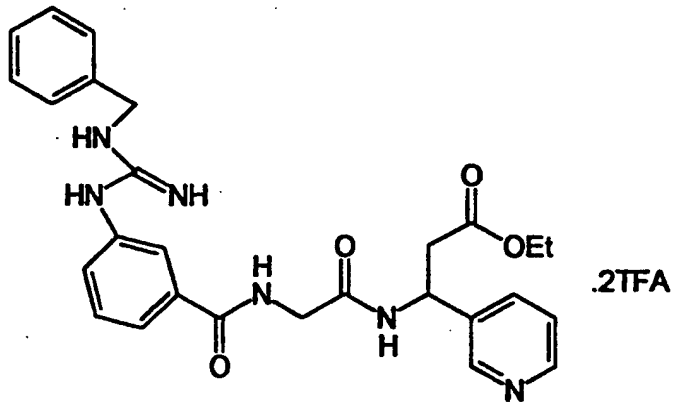


(RACEMIC)

The above compound was prepared according to the methodology of Example 12, substituting an equivalent amount of 3,5-diaminobenzoic acid dihydrochloride (0.3 equivalents) (Fluka) for 3-aminobenzoic acid hydrochloride in Example 11, Step A. MS and NMR were consistent with the desired structure.

Example 23

Preparation of (±) ethyl β-[[2-[[[3-[[imino-[(phenylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

1-(3-Carboxyphenyl)-2-thiourea (5 g, 0.025 mole)(Trans World Chemicals) in THF (75 ml) and CH_3I (3.62 g, 0.025 mole) were stirred at reflux for 2 hours. The solvent was removed under vacuum and the residue was slurried in ether (3X), (the ether decanted off each time) to yield, after drying under vacuum, N-(3-carboxyphenyl)-S-methylisothiouronium hydroiodide (7.8 g) as a yellow solid.

Step B

To the product of Step A (1.5 g, 0.0044 mole) and diisopropylethylamine (0.57 g, 0.0044 mole) in H_2O (5 ml) and dioxane (5 ml) was added benzylamine (0.48 g, 0.0044 mole). The reaction mixture was heated at reflux for 6 hours. The reaction was cooled to room temperature and a precipitate formed. Dioxane (6 ml) was added and the slurry was stirred overnight at room temperature. The precipitate was filtered, washed with dioxane/H_2O, dried, slurried in H_2O, and acidified with concentrated HCl. The solvent was removed under vacuum

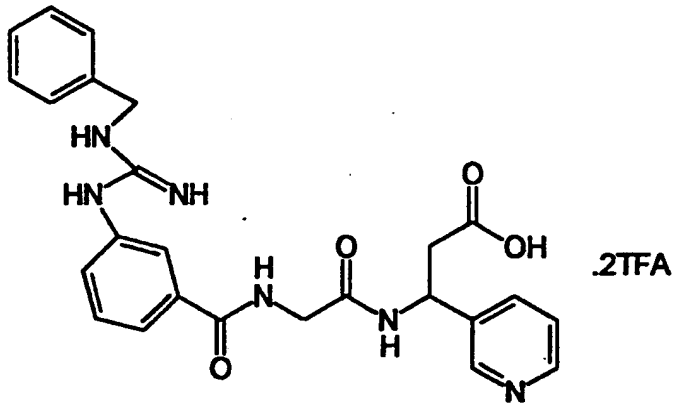
and the residue was slurried in ether (3X; ether decanted off each time). After drying, 1-(3-carboxyphenyl)-2-benzylguanidine hydrochloride (800 mg) was isolated as a white solid. MS and NMR were consistent with the desired structure.

Step C

The title compound was prepared according to Example 1, Step F, substituting an equivalent amount of the product from Step B above for the product from Example 1, Step E in Step F. MS and NMR were consistent with the desired structure.

Example 24

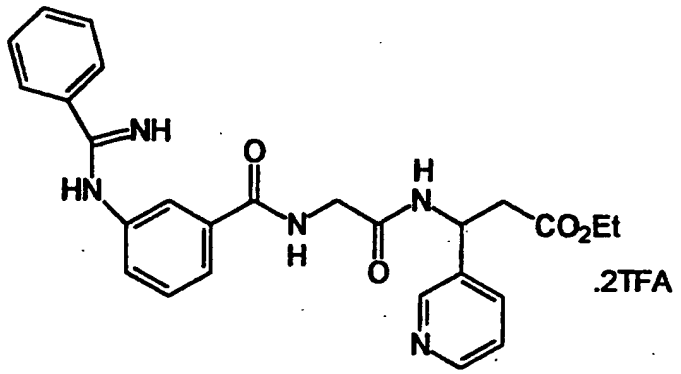
Preparation of (±) β-[[2-[[[3-[[imino[(phenylmethyl)-amino]methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 23, Step C (330 mg, 0.00045 mole) in H_2O (20 ml) was added LiOH (80 mg). The reaction was stirred at room temperature for 1 hour. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[3-[[imino[(phenylmethyl)amino]methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (330 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 25

Preparation of (±) ethyl β-[[2-[[[3-[(iminophenylmethyl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

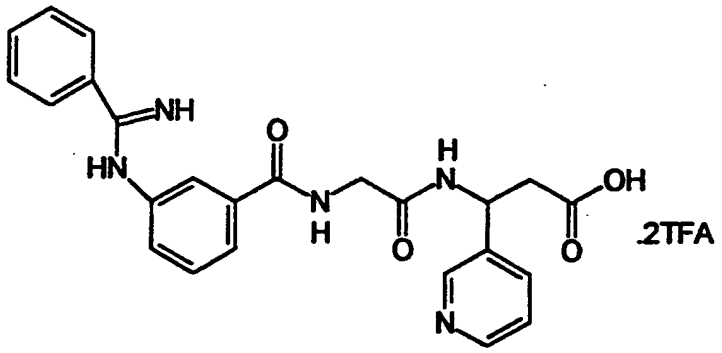
To ethyl benzimidate hydrochloride (3 g, 0.016 mole)(Fluka) and (2.1 g, 0.016 mole) diisopropylethylamine in H_2O (15 ml) and dioxane (15 ml) was added 3-aminobenzoic acid (2.22 g, 0.016 mole) (Aldrich). The reaction mixture was stirred at room temperature for 4 days. The resulting precipitate was filtered, washed with dioxane/H_2O and dried. The precipitate was slurried in H_2O and acidified with concentrated HCl. The solvent was removed under vacuum and the residue was slurried in ether. The ether was decanted off and the residue dried under vacuum to yield N-(3-carboxyphenyl)benzamidine hydrochloride (700 mg) as a white solid. MS and NMR were consistent with the desired structure.

Step B

The title compound was prepared according to the methodology of Example 1, Step F, substituting an equivalent amount of the product from Step A above for the product from Example 1, Step E in Step F. MS and NMR were consistent with the desired structure.

Example 26

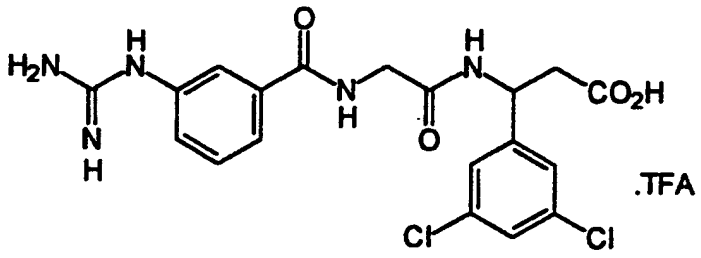
Preparation of (±) β-[[2-[[[3-[(iminophenylmethyl]-amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 25, Step B (240 mg, 0.0034 mole) in H_2O (20 ml) was added LiOH (50 mg). The reaction mixture was stirred at room temperature for 35 minutes. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[3-[(iminophenylmethyl]amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (120 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 27

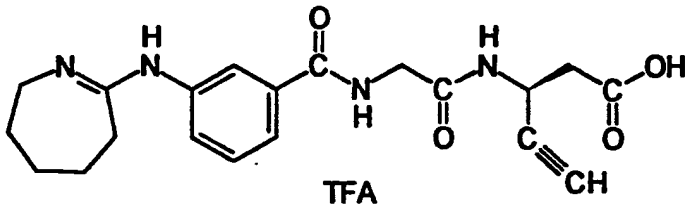
Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt



The above compound was prepared according to the method of Example 2 substituting an equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A.

Example 30

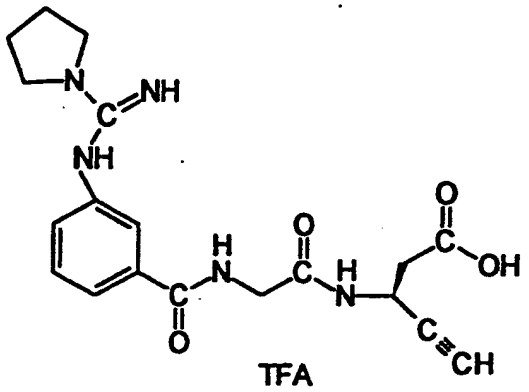
Preparation of βS-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



The above compound was prepared according to the method of Example 12, substituting an equivalent amount of ethyl 3-S-amino-4-pentynoate hydrochloride (J. Med. Chem. 1995, 38, 3378-2394) for ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride in Example 1, Step C and further used in Example 1, Step D as described in Example 11, Step B.

Example 34

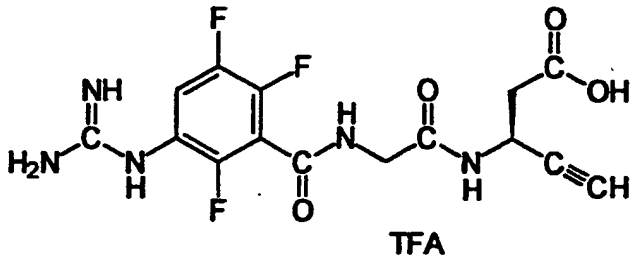
Preparation of βS-[[2-[[[3-[[imino(1-pyrrolidinyl)-methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



The above compound was prepared according to methodology of Example 24, substituting an equivalent amount of pyrrolidine for benzylamine in Example 23, Step B and an equivalent amount of ethyl 3-S-amino-4-pentynoate hydrochloride for ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride in Example 1, Step C and further used in Example 1, Step D as described in Example 23, Step C.

Example 35

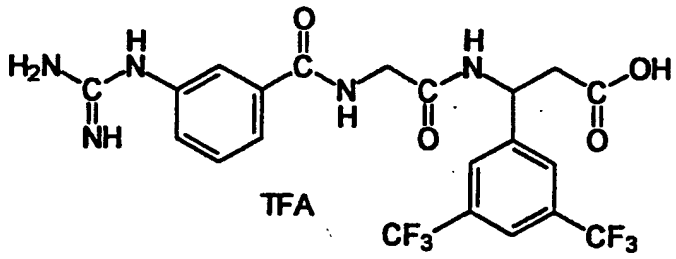
Preparation of βS-[[2-[[[3-[(aminoiminomethyl)amino]-2,5,6-trifluorophenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 2, substituting an equivalent amount of ethyl 3-S-amino-4-pentynoate hydrochloride for ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride in Example 1, Step C and substituting an equivalent amount of 3-amino-2,5,6-trifluorobenzoic acid for 3-aminobenzoic acid in Example 1, Step E.

Example 36

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt



Step A

Preparation of ethyl (±) β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-bis(trifluoromethyl)benzenepropanoate.

The above compound was prepared according to the methodology of Example 1, substituting the equivalent amount of 3,5-bis-trifluoromethylbenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Step A.

NMR and mass spectrometry were consistent with the desired structure.

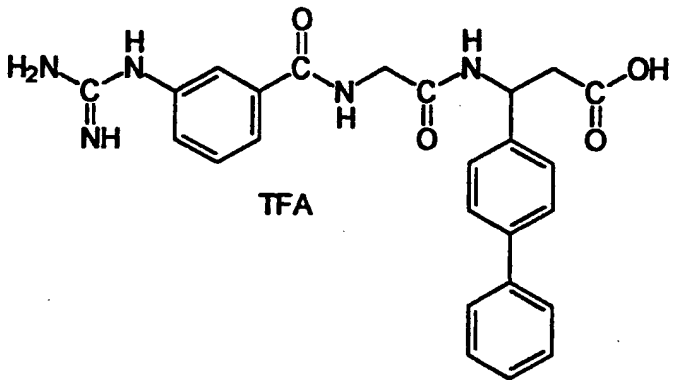
Step B

To 260 mg (0.00039 mole) of the product of Step A above in H_2O (25 ml) and CH_3CN (10 ml) was added LiOH (41 mg, 0.00098 mole). The reaction was stirred at room temperature for 1 hour. The pH was lowered to 3 with TFA and the product was isolated by reverse phase prep HPLC to yield (after lyophilization) 210 mg of the title compound as a white solid.

NMR and mass spectrometry were consistent with the desired structure.

Example 37

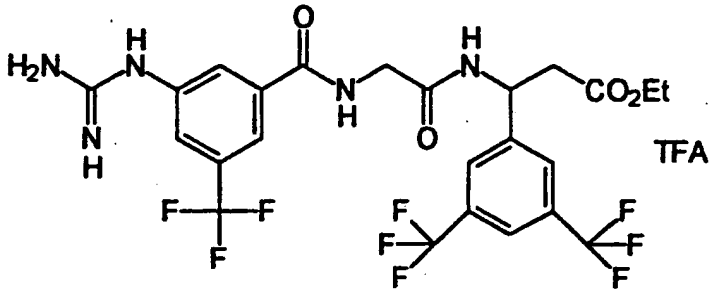
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino][1,1'-biphenyl]-4-propanoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 2, substituting an equivalent amount of 4-biphenylcarboxaldehyde for 3-pyridinecarboxaldehyde in Example 1, Step A.

Example 38

Preparation of (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)amino]-5-(trifluoromethyl)-phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoate, trifluoroacetate salt

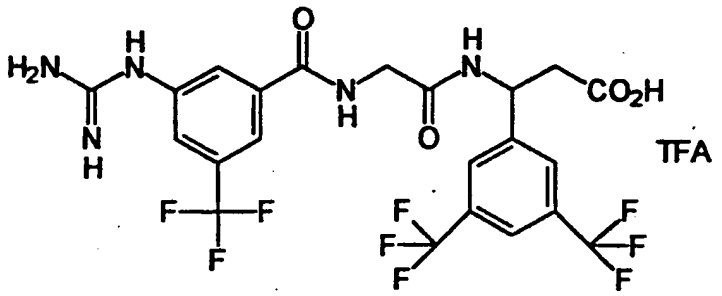


The above compound was prepared according to the methodology of Example 1, substituting the equivalent amount of 3,5-bis-trifluoromethylbenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Step A and substituting the equivalent amount of 3-amino-5-trifluoromethylbenzoic acid [which was synthesized by reduction of 3-nitro-5-trifluoromethylbenzoic acid (Lancaster) in ethanol with 10% Pd/C under 50 psi H_2 for 4 hours] for 3-aminobenzoic acid in Step E and stirring the resulting reaction mixture from Step E at reflux overnight instead of 2.5 hours.

NMR and mass spectrometry were consistent with the desired structure.

Example 39

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]-acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt

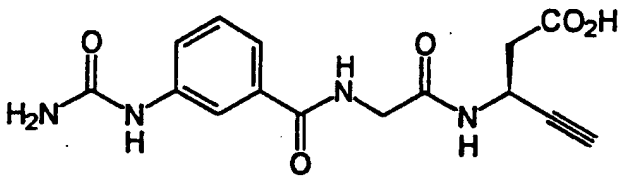


To 600 mg (0.00082 mole) of the product of Example 38 in 12 ml of H_2O and 12 ml of CH_3CN was added 140 mg (0.0033 mole) of LiOH. The reaction was stirred at room temperature for 1.5 hours. The pH was lowered to 2.5 with TFA and the product isolated by reverse phase prep HPLC to yield (after lyophilization) 520 mg of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt as a white solid.

NMR and mass spectrometry were consistent with the desired structure.

Example 40

Preparation of 3S-[[2-[[[3-(aminocarbonylamino)-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid



Step A

Ethyl 3S-amino-4-pentynoate hydrochloride was prepared using the method in J. Med. Chem. 1995, 38, 3378-94.

Step B

2 g m-aminohippuric acid in 5% aqueous HCl (25 ml) was treated with urea (2 g) and the solution was refluxed for 4 hours. m-N-carbamoylaminohippuric acid was purified by HPLC (RP-CH_3CN/H_2O) and lyophilized to give 1.2 g of white solid. The MS was consistent with the desired product.

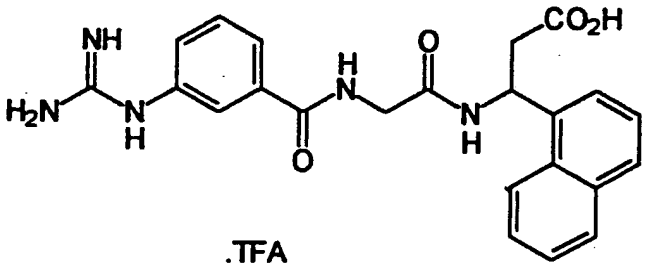
Step C

A suspension of m-ureahippuric acid (1.2 g) in DMF (5 ml) and pyridine (5 ml) was treated with DSC (1.5 g). A catalytic amount of DMAP was added and the reaction mixture was stirred for 3 hours. A solution of 3S-aminopentynoic acid, hydrochloride (0.8 g) and K_2CO_3 (0.7 g) in saturated aqueous $NaHCO_3$ (5 ml) was added to the reaction mixture. The resulting mixture was stirred overnight at room temperature. The reaction was diluted to 45 ml with 1:1 $CH_3CN:H_2O$ and acidified with of trifluoracetic acid (5 ml). The ester was purified by HPLC (RP-CH_3CN/H_2O) and a white solid (125 mg) was recovered after lyophilization. This material was then treated with 1:1 $CH_3CN:H_2O$ (20

ml) and made basic (pH>12) with LiOH. After complete reaction, the product was purified by HPLC ($RP-CH_3CN/H_2O$) and the desired product (60 mg) was obtained. MS, ^1H-NMR and CHN analysis were consistent with the desired product.

Example 41

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]naphthalene-1-propanoic acid, trifluoroacetate salt



.TFA

Step A

A mixture of freshly distilled 1-napthalenecarboxaldehyde (8.6 g), ammonium acetate (10.6 g) and malonic acid (5.7 g) in isopropyl alcohol (50 ml) was refluxed for 4 hours. The reaction was filtered while hot and washed with hot isopropyl alcohol (2 x 50 ml), washed with H_2O (125 ml) and isopropanol (100 ml) and dried *in vacuo* at 40°C. 4.6 g of βS-aminonaphthalene-1-propanoic acid as a white solid was isolated. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A suspension of the product of Step A (4.6 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight and the excess solvent was removed under reduced pressure. The oil was dissolved into 1:1 CH_3CN:H_2O and purified by HPLC (RP-CH_3CN/H_2O). Methyl βS-aminonaphthalene-1-propanoate (4.6 g) as a white solid was obtained. MS and ^{1}H-NMR were consistent with the desired product.

Step C

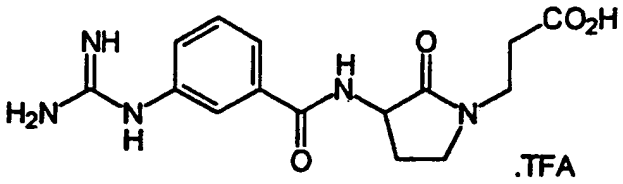
A suspension of m-guanidinohippuric acid HCl (1.4 g) in DMF (5 ml) and pyridine (5 ml) was treated with DSC (3 g) and a catalytic amount of DMAP. The reaction was stirred overnight at room temperature. The resulting solution was treated with a solution of the product of Step B (1.7 g) and NMM (0.6 ml) in DMF (2.5 ml) and pyridine (2.5 ml). The mixture was stirred overnight at room temperature. The reaction was then treated with TFA and diluted to 50 ml with 1:1 $CH_3CN:H_2O$. The solution was purified by HPLC (RP-CH_3CN/H_2O) and (±) methyl βS-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]naphthalene-1-propanoate (1.3 g) as a white solid was obtained after lyophilization. MS and ^{1}H-NMR were consistent with the desired product.

Step D

A solution of the product of Step C (0.5 g) in 1:1 $CH_3CN:H_2O$ (15 ml) was treated with LiOH until pH > 12. The reaction was monitored by HPLC (RP-CH_3CN/H_2O) and when hydrolysis was complete, the desired material was purified by HPLC (RP-CH_3CN/H_2O). A white solid (0.3 g) was recovered after lyophilization. MS, ^{1}H-NMR and CHN were consistent with the desired product.

Example 42

Preparation of (±) 3-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]-2-oxopyrrolidine-1-propanoic acid, trifluoroacetate salt

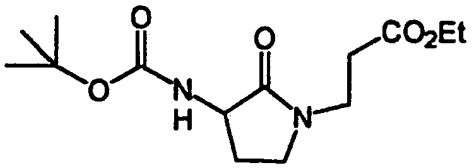


Step A

A solution of N-(tert-butoxycarbonyl)-L-methionine (6.2 g) in DMF (25 ml) and pyridine (25 ml) was treated with DSC (9.6 g) and a catalytic amount of DMAP. After 4 hours, a solution of β-alanine ethyl ester HCl (3.8 g) and K_2CO_3 (3.5 g) in saturated aqueous $NaHCO_3$ (25 ml) was added. The reaction mixture was stirred overnight at room temperature. The excess solvent was removed under reduced pressure and purified by HPLC (RP-CH_3CN/H_2O). N-[2-[[(1,1-dimethylethoxy)carbonyl]-amino]-4-(methylthio)-1-oxobutyl]-β-alanine, ethyl ester (7.0 g) as a colorless oil was obtained. The oil was confirmed as the desired product by MS and used without further purification.

Step B

6.5 g of the oil from Step A was dissolved in DMF (25 ml) and treated with CH_3I (5.0 ml). After approximately 1 hour, NaH (0.50 g) was added, followed by further addition of NaH (0.50 g). The reaction was treated with H_2O (25 ml) and EtOAc (200 ml). The organic layer was washed with additional H_2O (3 x 25 ml), saturated aqueous NaCl (1 x 25 ml) and dried over $NaSO_4$. The excess solvent was removed under reduced pressure to give 4 g of



as a tan semi-solid. MS was consistent with the structure and the product was used without further purification.

Step C

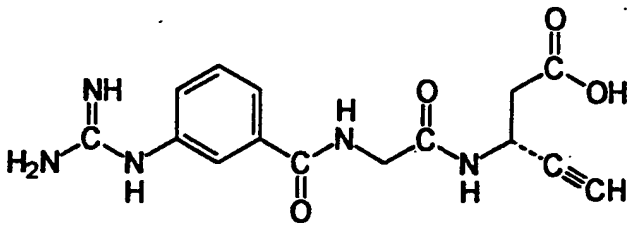
A solution of the product of Step B (4 g) in ethanol (50 ml) was treated with 4N HCl/dioxane (20 ml). The excess solvent was removed under reduced pressure. The crude solid was purified by HPLC (RP-CH_2CN/H_2O). 20% aqueous HCl (10 ml) was added and 1 g of ethyl 3-amino-2-oxopyrrolidine-1-propanoate was obtained as a white solid after lyophilization. MS was consistent with the desired product.

Step D

A solution of m-guanidinobenzoic acid HCl (0.7 g) in DMF (3 ml) and pyridine (3 ml) was treated with DSC (0.8 g) and a catalytic amount of DMAP. After 3 hours a solution of the product of Step C (0.7 g) in H_2O (3 ml) with an equal molar amount of K_2CO_3 was added. The reaction was stirred overnight at room temperature. The desired ester was isolated by HPLC (RP-CH_3CN/H_2O). The white solid (100 mg) was treated with H_2O (10 ml) and made basic with LiOH (pH>12). After 2 hours, the desired product was isolated by HPLC (RP-CH_3CN/H_2O) and lyophilized. 75 mg of (±) 3-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]-2-oxopyrrolidine-1-propanoic acid, trifluoroacetate salt as a white solid was obtained. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 43

Preparation of 3R-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, hydrochloride salt



Step A

Ethyl 3-(N-(tert-butoxycarbonyl)amino)pent-4-ynoic ester (3 g) [J. Med. Chem., 1995, 38, 3378-94] in CH_2Cl_2 (60 ml) at 0°C was treated with TFA (30 ml). The reaction was stirred for 3 hours. The excess solvent was removed under reduced pressure and a yellow oil (3.3 g) was obtained. The oil was confirmed as the desired product by MS.

Step B

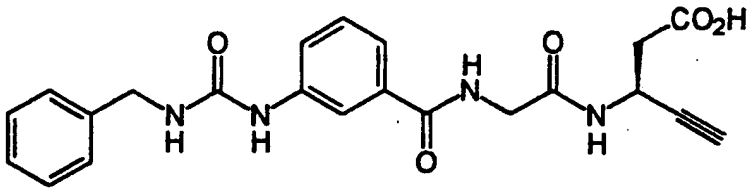
A solution of m-guanidinohippuric acid HCl (3.3 g) in DMF (12 ml) and pyridine (12 ml) was treated with DSC (6.1 g) and a catalytic amount of DMAP. After 3 hours, a solution of crude product (3.3 g) from Step A in saturated aqueous $NaHCO_3$ (12 ml) was added. The reaction was stirred overnight at room temperature. The excess solvent was removed under reduced pressure. The resulting solid was treated with TFA and 1:1 $CH_3CN:H_2O$. The product was isolated by HPLC (RP-CH_3CN/H_2O) to yield ethyl 3R-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]propynoate trifluoroacetate salt (3 g) as a white solid. MS and ^1H-NMR were consistent with the desired product.

Step C

The product of Step B (3 g) was dissolved in 1:1 $CH_3CN:H_2O$ (50 ml) and treated with LiOH (pH>12). After 4 hours the reaction was acidified with TFA and the TFA salt of the desired product was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (2.5 g) was slurried with 1:3 $CH_3CN:H_2O$ (100 ml) and ion exchange resin, AG 2-X8 chloride form (BioRad)(50 g). The mixture was filtered and treated with 20% HCl (5 ml). The clear solution was lyophilized and the resin exchange process was repeated. The desired product (2.2 g) was obtained. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 44

Preparation of 3S-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid



Step A

m-Aminohippuric acid HCl (20 g) in CH_3CN (100 ml) was treated with benzyl isocyanate (16 ml). The reaction was treated with 5% aqueous HCl (400 ml), filtered and washed with H_2O (50 ml) to give 21 g of m-(benzylurea)hippuric acid. The MS and ^{1}H-NMR were consistent with the desired product. No further purification was done.

Step B

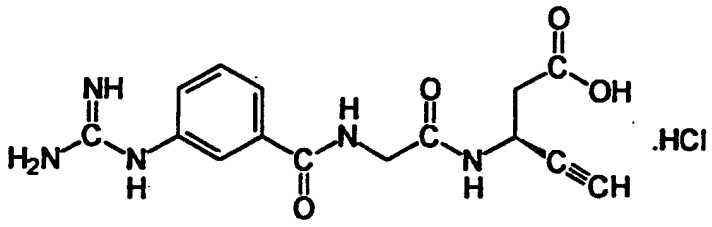
Ethyl 3S-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoate was prepared using the method in Example 40 substituting an equal molar amount of m-(benzylurea)hippuric acid for m-ureahippuric acid. The desired ester was purified by HPLC (RP - CH_3CN/H_2O) to give 1.2 g as a white solid. The MS and ^{1}H-NMR were consistent with the desired ester.

Step C

A solution of ethyl 3S-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]-4-pentynoate (1.0 g) in 1:1 $CH_3CN:H_2O$ (20 ml) was treated with KOH (pH>12). After 4 hours the reaction was acidified with TFA and purified twice by HPLC (RP-CH_3CN/H_2O). A white solid (300 mg) was obtained. MS, ^{1}H-NMR and CHN were consistent with the desired product.

Example 45

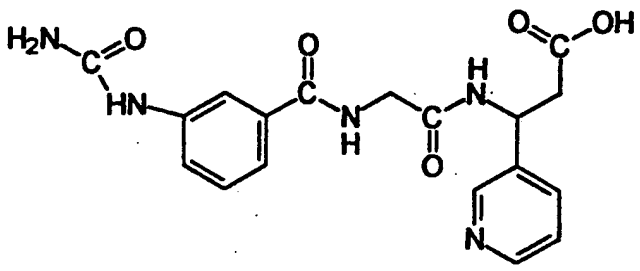
Preparation of 3S-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, hydrochloride salt



The product of Example 58 (6 g) was dissolved in 1:1 $CH_3CN:H_2O$ (75 ml) and treated with KOH. The pH was maintained greater than 12 by addition of KOH. After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The TFA salt (4.2 g) was obtained after the appropriate fractions were lyophilized. The solid was slurried in 1:1 $CH_3CN:H_2O$ (100 ml) and treated with ion exchange resin AG 2-X8 chloride form (BioRad) (50 g). The mixture was filtered and treated with 20% HCl (5 ml). After lyophilization the resin exchange was repeated. The desired product as the HCl salt (3.5 g) was obtained. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 46

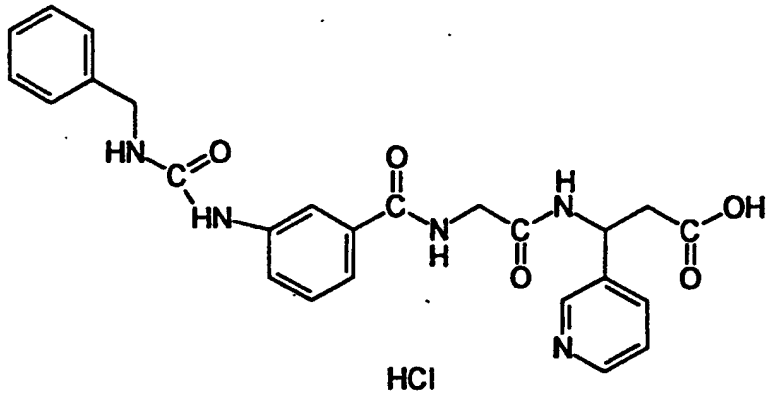
Preparation of β-[[2-[[[3-(aminocarbonylamino)phenyl]-carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, hydrochloride salt



Urea (4 g) and ethyl β-[[2-[[(3-aminophenyl)-carbonyl]amino]acetyl]amino]pyridine-3-propanoate trifluoroacetate salt (4 g) were dissolved in 20% aqueous HCl (50 ml) and refluxed for 6 hours. The reaction was made basic with KOH (pH>12). After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The white solid was dissolved in 1:1 $CH_3CN:H_2O$ (100 ml) and subjected to the resin exchange described in Example 43, Step C. Lyophilization gave the desired product (3.2 g). MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 47

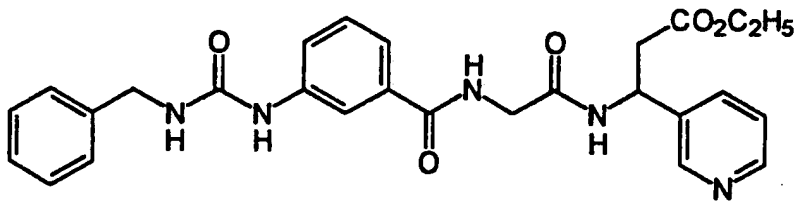
Preparation of (±) β-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, hydrochloride salt



The product of Example 48 (5 g) was dissolved in 1:1 $CH_3CN:H_2O$ (75 ml) and treated with KOH. The pH was maintained greater than 12 by addition of KOH. After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The TFA salt (4.5 g) was obtained after lyophilization. The solid was slurried in 1:1 $CH_3CN:H_2O$ (100 ml) and ion exchange resin, AG 2-X8 chloride form (BioRad)(50 g). The mixture was filtered and treated with 20% HCl (5 ml). After lyophilization the resin exchange process was repeated. The desired product (4.1 g) was obtained as a white solid. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 48

Preparation of (±) ethyl β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoate, hydrochloride salt



Step A

A solution of m-nitrohippuric acid (5.6 g) in DMF (25 ml) was treated with DSC (9.6 g) and a catalytic amount of DMAP. After 5 hours, a solution of ethyl 3-amino-3-(3-pyridyl)propanoate 2HCl (8 g) and K_2CO_3 (2 g) in saturated aqueous $NaHCO_3$ (25 ml) was added. The reaction mixture was stirred overnight at room temperature. H_2O (25 ml) was added and the mixture was filtered. The resulting solid was washed with H_2O (25 ml), slurried with CH_3CN (25 ml) and filtered. Ethyl β-[[2-[[(3-nitrophenyl)carbonyl]amino]acetyl]amino]pyridine-3-propanoate (6.5 g) was obtained as a white solid. MS was consistent with the desired product.

Step B

A suspension of the product of Step A (6.5 g) and 5% Pd/C (0.6 g) in H_2O (50 ml) and ethanol (50 ml) was subjected to 50 psi H_2 for 3 hours. The mixture was filtered through a celite pad and the excess solvent was removed under reduced pressure. The resulting oil was treated with CH_2Cl_2 and the solvent was again removed under reduced pressure. Ethyl β-[[2-[[(3-aminophenyl)carbonyl]amino]acetyl]amino]pyridine-3-

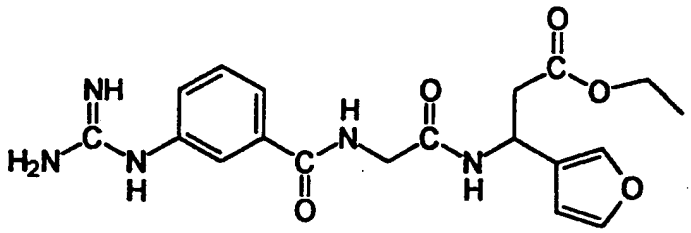
propanoate (5.8 g) was recovered as a tan foam. MS and ^{1}H-NMR were consistent with the desired product.

Step C

A solution of the product of Step B (1.9 g) in CH_3CN (5 ml) was treated with benzyl isocyanate (0.8 ml). After 1 hour benzyl isocyanate (0.1 ml) was added to complete the reaction. After 0.25 hour the reaction was treated with H_2O (50 ml). The resulting viscous oil was dissolved in CH_3CN and was acidified with TFA. The solution was purified by HPLC (RP-CH_3CN/H_2O) and lyophilized. The white solid was repurified by HPLC (RP-CH_3CN/H_2O) and treated with 20% HCl (5 ml). The desired product (1.3 g) was obtained as a white solid. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 51

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-3-propanoate, trifluoroacetate salt



.TFA

Step A

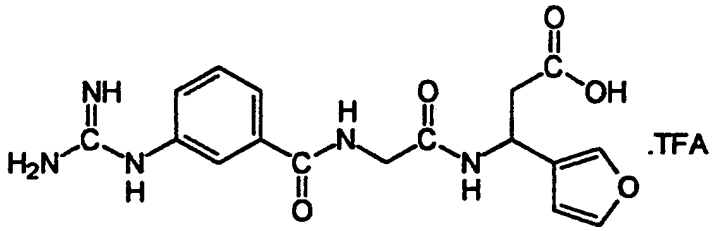
A suspension of 3-furancarboxaldehyde (8.6 ml), malonic acid monoethyl ester (15.8 g) and ammonium acetate (9.6 g) in isopropyl alcohol (200 ml) was heated to reflux under nitrogen. After 5 hours, the excess solvent was removed under reduced pressure and the semi-solid was treated with H_2O (250 ml) and acidified to pH 2 using 12N HCl. The aqueous layer was washed with CH_2Cl_2 (2 x 100 ml). The aqueous layer was neutralized to pH >9 with K_2CO_3. The product was extracted with CH_2Cl_2 (2 x 100 ml). The organic layer was dried over Na_2SO_4 and the excess solvent was removed under reduced pressure to give ethyl β-aminofuran-3-propanoate (5 g) as a golden oil. The MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (1.4 g) in DMF (5 ml) and pyridine (5 ml) was treated with DSC (1.9 g) and a catalytic amount of DMAP. After 5 hours, to a solution of the product of Step A (1.2 g) in CH_3CN (1 ml) was added saturated aqueous $NaHCO_3$ (1 ml). The mixture was stirred overnight at room temperature and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (1.2 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 52

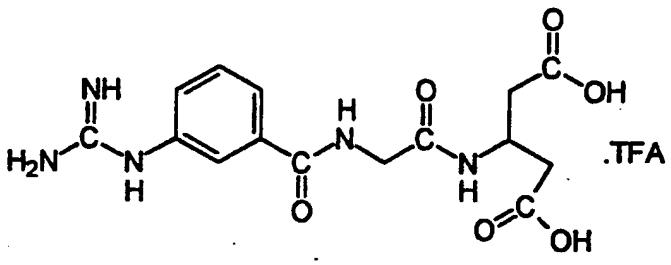
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-3-propanoic acid, trifluoroacetate salt



The product of Example 51 (0.6 g) was dissolved in 1:1 $CH_3CN:H_2O$ (15 ml) and was treated with NaOH (pH>12). After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (0.3 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 53

Preparation of 3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pentanedioic acid, trifluoroacetate salt



Step A

Dimethyl 3-ketoglutarate (13 g) in methanol (50 ml) was treated with ammonium formate (5 g) and $NaCNBH_3$ (2 g). 10 ml of H_2O was added and the excess solvent removed under reduced pressure. The semi-solid was dissolved in 5% aqueous HCl (250 ml), and washed with CH_2Cl_2 (2 x 50 ml). The aqueous layer was made basic (pH>9) with K_2CO_3 and the product was extracted using CH_2Cl_2 (2 x 75 ml). The organic layers were combined and dried with Na_2SO_4. The excess solvent was removed to give 2.5 g of the dimethyl (±)3-aminoglutarate. This was dissolved in methanol (50 ml) and treated with 4N HCl/Dioxane (10 ml). The excess solvent was removed under reduced pressure to give a 2.7 g of dimethyl (±)3-aminoglutarate hydrochloride. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (1.5 g) in DMF (4.5 ml) and pyridine (4.5 ml) was treated with DSC (1.8 g) and a catalytic amount of DMAP. After 2 hours, a solution of dimethyl 3-aminoglutarate HCl (1.1 g) and NMM (350 μl) in H_2O (3 ml) was added to the reaction. The reaction was stirred overnight at room temperature and the product was isolated by HPLC. 1.5 g of 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]-

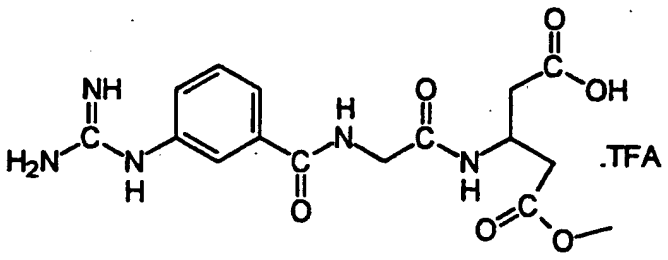
carbonyl]amino]acetyl]amino]pentanedioic acid, bismethyl ester was obtained as a white solid. MS and ^{1}H-NMR were consistent with the desired product.

Step C

The product of Step B (750 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (40 ml) and treated with KOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (400 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 54

Preparation of (±) hydrogen methyl 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]pentanedioate, trifluoroacetate salt



Step A

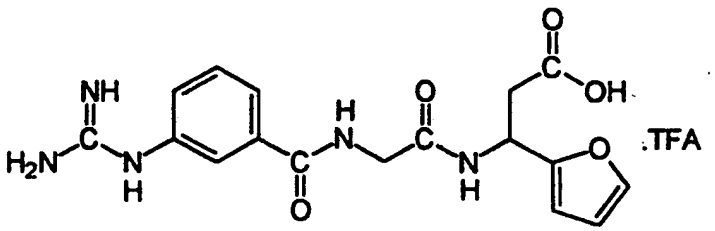
A solution of m-guanidinohippuric acid HCl (1.5 g) in DMF (4.5 ml) and pyridine (4.5 ml) was treated with DSC (1.8 g) and a catalytic amount of DMAP. After 2 hours, a solution of dimethyl 3-aminoglutarate HCl (1.1 g) and NMM (350 µl) in H_2O (3 ml) was added to the reaction. The reaction was stirred overnight at room temperature and the product was isolated by HPLC. 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]-amino]acetyl]amino]pentanedioic acid, bis methyl ester (1.5 g) as a white solid was obtained. MS and ^{1}H-NMR were consistent with the desired product.

Step B

750 mg of the product of Step A was dissolved in Na_2PO_4 buffer (50 ml, 50 mM, pH 8.5) and treated with porcine esterase (200 µl). The pH was adjusted using LiOH. After 48 hours, the solution was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (175 mg) had MS, ^{1}H-NMR and CHN analysis consistent with the desired product.

Example 55

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-2-propanoic acid, trifluoroacetate salt



Step A

A suspension of 2-furancarboxaldehyde (4.8 g), ammonium acetate (9.6 g) and malonic acid monoethyl ester (6.6 g) in isopropanol (50 ml) was refluxed for 6 hours. The excess solvent was removed under reduced pressure and the resulting oil was treated with ethyl acetate (100 ml) and 5% aqueous HCl (400 ml). The aqueous layer was then washed with ethyl acetate (100 ml). The aqueous layer was made basic with K_2CO_3 (pH 9). The product was extracted with CH_2Cl_2 (2 x 100 ml). The organic layers were combined and dried with Na_2SO_4 and the excess solvent was removed. Ethyl β-aminofuran-2-propanoate (2.5 g) as a dark oil was recovered. MS and ^{1}H-NMR were consistent with the desired product. The dark oil was treated as described in Example 53, Step A to give 2.7 g of ethyl β-aminofuran-2-propanoate hydrochloride.

Step B

A solution of m-guanidinohippuric acid HCl (272 mg) in DMF (1 ml) and pyridine (1 ml) was treated with DSC (450 mg) and a catalytic amount of DMAP. After 2 hours, a solution of the product of Step A (221 mg), NMM (111 μl) in H_2O (1 ml) and CH_3CN (1 ml) was added. The reaction was stirred overnight at room temperature.

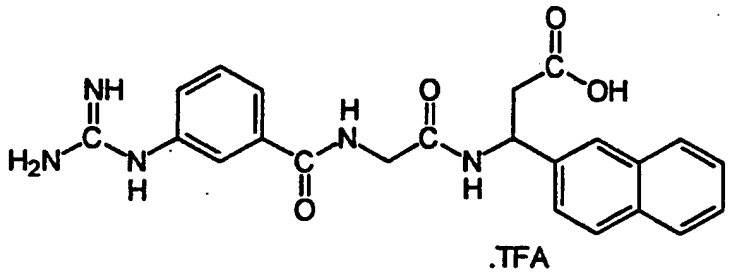
(±) Ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-2-propanoate was purified by HPLC (RP-CH_3CN/H_2O) and lyophilized to give a white solid (200 mg). MS was consistent with the desired product.

Step C

The product of Step B (200 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (20 ml) and treated with LiOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (175 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 56

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]naphthalene-2-propanoic acid, trifluoroacetate salt



Step A

A suspension of 2-naphthaldehyde (7.8 g) and ammonium acetate (9.6 g) in isopropyl alcohol (50 ml) was heated for 1 hour at reflux. Malonic acid (5.2 g) was added and reflux was continued for 3 hours. The reaction was filtered while hot and the solid washed with hot isopropyl alcohol (50 ml) followed by CH_3CN (100 ml). The white solid was dried overnight *in vacuo* and β-aminonaphthalene-2-propanoic acid (9 g) was recovered. MS and ^{1}H-NMR were consistent with the structure.

Step B

A suspension of the product of Step A (2.5 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The resulting solution was stirred overnight. The excess solvent was removed under reduced pressure and the semi solid was purified by HPLC (RP-CH_3CN/H_2O). The solid was dissolved in CH_3CN/H_2O, treated with 20% aqueous HCl (5 ml) and lyophilized to give methyl β-aminonaphthalene-2-propanoate hydrochloride (1.1 g). MS and ^{1}H-NMR were consistent with the structure.

Step C

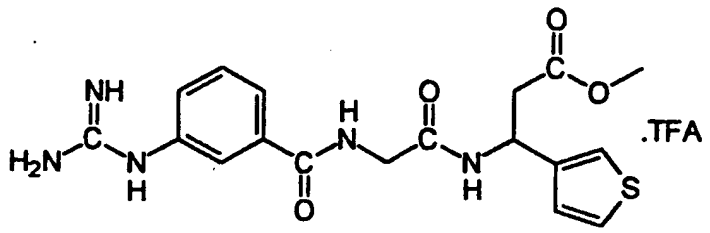
A solution of m-guanidinohippuric acid (0.7 g) in DMF (4 ml) and pyridine (4 ml) was treated with DSC (1.1 g) and a catalytic amount of DMAP. After 4 hours, a solution of the product of Step B (0.9 g), NMM (0.4 ml) in DMF (2 ml), pyridine (2 ml) and H_2O (1 ml) were added. The reaction was stirred overnight at room temperature and acidified with TFA. The desired product was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (0.7 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Step D

The product of Step C (200 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (20 ml) and treated with KOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (175 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 57

Preparation of (±) methyl β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]thiophene-3-propanoate, trifluoroacetate salt



Step A

A solution of 3-thiophenecarboxaldehyde (11.2 g) in isopropanol (100 ml) was treated with ammonium acetate (20 g). The resulting mixture was heated and malonic acid (10.4 g) was added. The reaction was refluxed for 4 hours and filtered while hot. The solid was washed with hot isopropanol (2 x 50 ml) and dried *in vacuo* overnight at 40°C. 8 g of β-aminothiophene-3-propanoic acid was recovered. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A suspension of the product of Step A (5 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight. The excess solvent was removed under reduced pressure. Methyl β-aminothiophene-3-propanoate hydrochloride (7.8 g) was isolated as a yellow foam. MS and ^{1}H-NMR were consistent with the desired product.

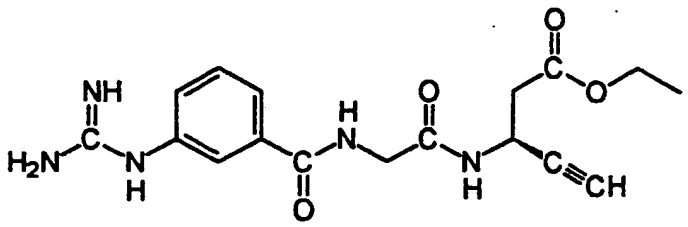
Step C

A solution of m-guanidinohippuric acid HCl (2.7 g) in DMF (10 ml) and pyridine (10 ml) was treated with DSC (4.5 g) and a catalytic amount of DMAP. After 4 hours, a solution of the product of Step B (2.2 g) and

NMM (1.3 ml) in DMF (5 ml) was added and the reaction was stirred overnight at room temperature. The reaction mixture was treated with 1:1 $CH_3CN:H_2O$ (50 ml) and acidified with TFA. The desired compound was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (2.2 g) had MS, ^1H-NMR and CHN analysis that were consistent with the desired product.

Example 58

Preparation of ethyl 3S-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoate, trifluoroacetate salt

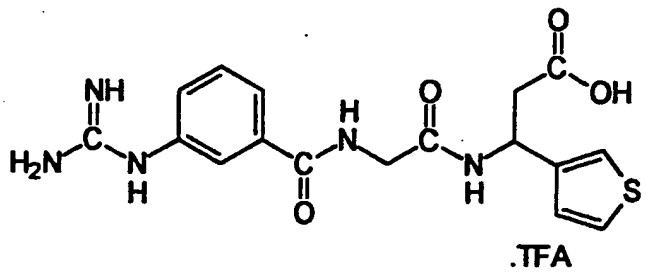


.TFA

A solution of m-guanidinohippuric acid HCl (2.7 g) in DMF (10 ml) and pyridine (10 ml) was treated with DSC (4.5 g) and a catalytic amount of DMAP. After 4 hours, a solution of ethyl 3S-amino-4-pentynoic acid, hydrochloride (1.8 g) and NMM (1.1 ml) in DMF (5 ml) was added and the reaction was stirred overnight at room temperature. The reaction mixture was treated with 1:1 $CH_3CN:H_2O$ (50 ml) and acidified with TFA. The desired compound was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (2.6 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 59

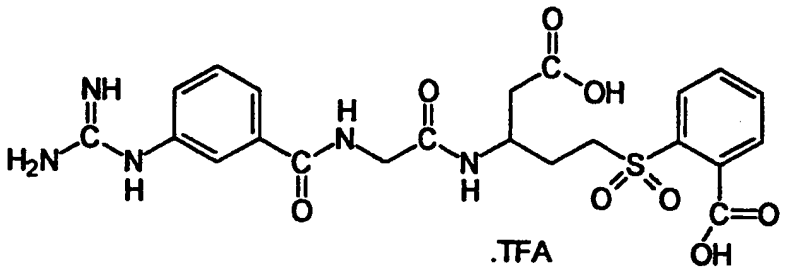
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]thiophene-3-propanoic acid, trifluoroacetate salt



The product of Example 57 (750 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (20 ml) and treated with KOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (500 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 60

Preparation of (±) 2-[3-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-carboxybutyl]sulfonyl]benzoic acid, trifluoroacetate salt



Step A

A solution of 2-[(3-amino-4-carboxybutyl)thio]-benzoic acid (1 g) (prepared according to U.S. 5,409,939) in methanol (50 ml) was treated with 4N HCl/dioxane (10 ml) overnight. The excess solvent was removed under reduced pressure to give the desired product (0.9 g). MS of the white solid, methyl 2-[(3-amino-4-(methoxycarbonyl)butyl]thio]benzoate was consistent with the proposed structure.

Step B

A solution of m-guanidinohippuric acid HCl (0.8 g) in DMF (3 ml) and pyridine (3 ml) was treated with DSC (1.2 g) and a catalytic amount of DMAP. After 2 hours, a solution of the product of Step A (1 g), NMM (0.3 ml) in DMF (3 ml) was added. The reaction was stirred overnight at room temperature. KOH was added until pH greater than 12. After 4 hours, the reaction was acidified and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid, (±) 2-[3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-4-carboxybutyl]thio]benzoic acid,

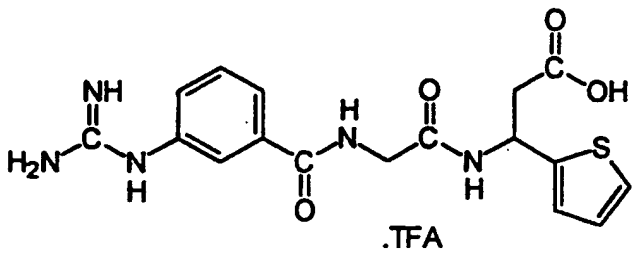
trifluoroacetate salt (750 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Step C

A solution of the product of Step B (320 mg) in 1:1 $CH_3CN:H_2O$ (50 ml) was treated with m-chloroperoxybenzoic acid (340 mg). The reaction was stirred overnight at room temperature and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (300 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 61

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]thiophene-2-propanoic acid, trifluoroacetate salt



Step A

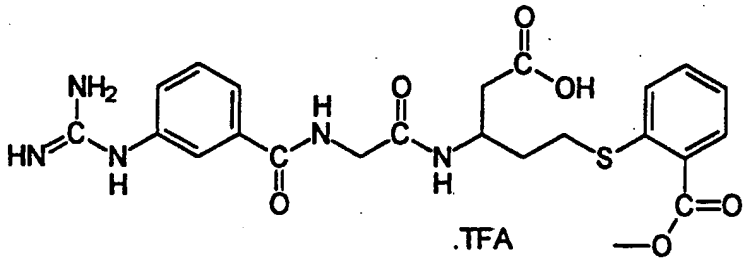
A solution of 3-amino-3-(2-thienyl)propanoic acid (0.5 g) [prepared substituting a molar equivalent amount of 2-thiophene-carboxaldehyde in Example 57, Step A] in methanol (50 ml) was treated with 4N HCl/dioxane (10 ml). After 6 hours the excess solvent was removed under reduced pressure to give a waxy solid. Treatment with Et_2O/CH_3CN produced methyl β-aminothiophene-2-propanoate (370 mg) as a white powder. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (0.4 g) in DMF (1.5 ml) and pyridine (1.5 ml) was treated with DSC (0.6 g) and a catalytic amount of DMAP. After 3 hours, a solution of the product of Step A (0.3 g) and NMM (220 μl) in DMF (1.5 ml) was added. The reaction was stirred overnight at room temperature. The ester was isolated by HPLC (RP-CH_3CN/H_2O) and lyophilized. The resulting white solid was treated with KOH (pH>12) in 1:4 $CH_3CN:H_2O$. After 4 hours, the reaction was acidified by TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (300 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 62

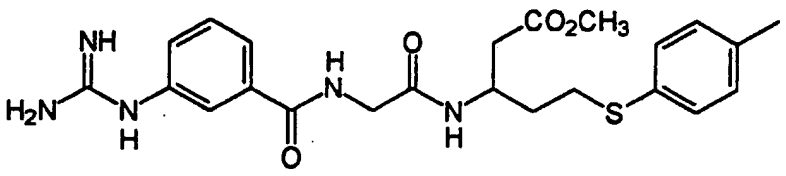
Preparation of (±) methyl 2-[[3-[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-4-carboxybutyl]thio]benzoate, trifluoroacetate salt



A solution of m-guanidinohippuric acid HCl (0.8 g) in DMF (3 ml) and pyridine (3 ml) was treated with DSC (1.2 g) and a catalytic amount of DMAP. After 2 hours, a solution of methyl 2-[[3-amino-4-(methoxycarbonyl)-butyl]thio]benzoate (1 g) [prepared according to U.S. 5,409,939], NMM (0.3 ml) in DMF (3 ml) was added. The reaction was stirred overnight at room temperature. KOH was added until the pH was greater than 12. After 2 hours, the reaction was acidified and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid, (250 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 63

Preparation of (±) methyl 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-5-[(4-methylphenyl)thio]pentanoate, trifluoroacetate salt



Step A

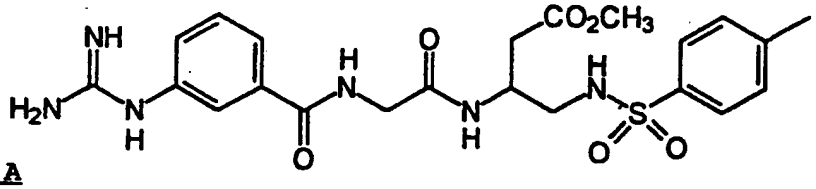
A solution of 3-amino-5-[(4-methylphenyl)-thio]pentanoic acid (1.0 g) [prepared according to U.S. 5,409,939] in methanol (50 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight at room temperature. The excess solvent was removed under reduced pressure. Methyl 3-amino-5-[(4-methylphenyl)thio]pentanoate (1.1 g) as a white solid was obtained. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (0.6 g) in DMF (2 ml) and pyridine (2 ml) was treated with DSC (0.7 g) and a catalytic amount of DMAP. After 1 hour, a solution of the product of Step A (0.6 g) in saturated aqueous $NaHCO_3$ (1.5 ml) and acetonitrile (1.5 ml) was added. The reaction was stirred for 2 hours at room temperature. The reaction was acidified with TFA and the title compound (0.6 g) was isolated by HPLC as a white solid. MS and ^{1}H-NMR were consistent with the desired product.

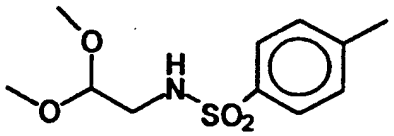
Example 64

Preparation of (±) methyl 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-4-[[(4-methylphenyl)sulfonyl]amino]butanoate, trifluoroacetate salt



Step A

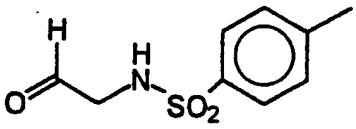
A mixture of aminoacetaldehyde dimethyl acetal (15.8 g), p-toluenesulfonylchloride (19.1 g) and Et_3N (10.1 g) in CH_2Cl_2 (200 ml) was stirred for 2 hours. The reaction was treated with 5% aqueous HCl (50 ml) and Et_2O (200 ml). The layers were separated and the organic layer was washed with 5% aqueous HCl (50 ml), H_2O (50 ml) and dried over Na_2SO_4. The excess solvent was removed under reduced pressure to give 30 g of the desired acetal;



confirmed by MS and ^{1}H-NMR.

Step B

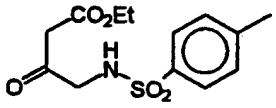
A mixture of the acetal from Step A (10 g), CH_3CN (70 ml) and aqueous HCl (15 ml) was heated to 50°C for 10 minutes. Diethylether was added and the desired aldehyde was extracted. The aldehyde was then used without further purification. The desired aldehyde



was verified by MS.

Step C

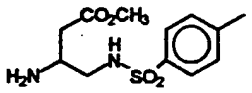
A mixture of ethyldiazoacetate (2.3 g), $SnCl_2$ (2.5 g) in CH_2Cl_2 (75 ml) was treated with the aldehyde from Step B (5 g). After 2 hours, aqueous HCl and Et_2O were added. The organic layer was separated and dried with $MgSO_4$. The solvent was removed under reduced pressure to yield 5 g of crude β-keto ester



; confirmed by MS and ^{1}H-NMR and used without further purification.

Step D

The β-keto ester from Step C (12 g), methanol (100 ml), H_4N^+ HCO_2^- (30 g) and $NaCNBH_3$ (1.3 g) was stirred. After 24 hours, the excess solvent was removed under reduced pressure. The resulting semi-solid was treated with CH_2Cl_2 and the desired product was extracted using aqueous HCl. Removal of the solvent gave 6 g of crude β-amino ester



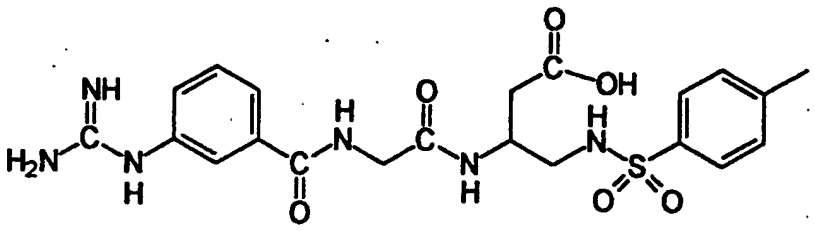
. ; confirmed by MS and ^{1}H-NMR.

Step E

A solution of m-guanidinohippuric acid HCl (337 mg) in DMF (1 ml) and pyridine (1 ml) was treated with DSC (0.4 g) and a catalytic amount of DMAP. After 2 hours, a solution of the product of Step D (322 mg) and NMM (220 μl) in DMF (1 ml) was added. The reaction was stirred overnight at room temperature. The reaction was acidified with TFA and the title compound (250 mg) was isolated by HPLC (RP-CH_3CN/H_2O) as a white solid. MS, CHN and ^{1}H-NMR were consistent with the desired product.

Example 65

Preparation of 3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-[[(4-methylphenyl)sulfonyl]amino]butanoic acid, trifluoroacetate salt

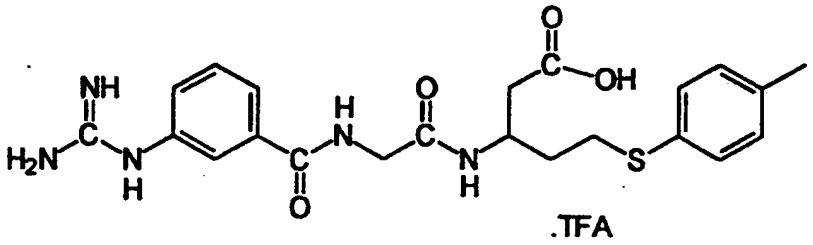


.TFA

A solution of the product of Example 64 (180 mg) in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with LiOH (100 mg). After 2 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The title compound (100 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 66

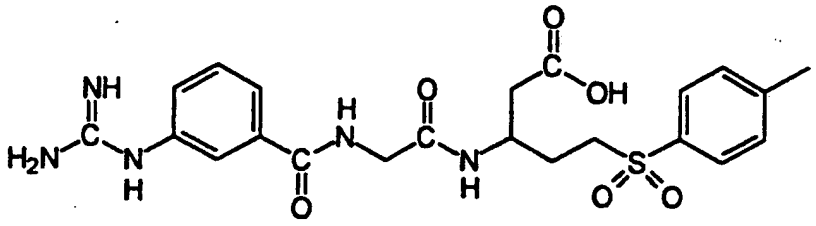
Preparation of (±)3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-[(4-methylphenyl)thio]pentanoic acid, trifluoroacetate salt



A solution of 180 mg of the product from Example 63 in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with LiOH (100 mg). After 2 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-5-[(4-methylphenyl)thio]pentanoic acid, trifluoroacetate salt (100 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 67

Preparation of (±)3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-[(4-methylphenyl)sulfonyl]pentanoic acid, trifluoroacetate salt

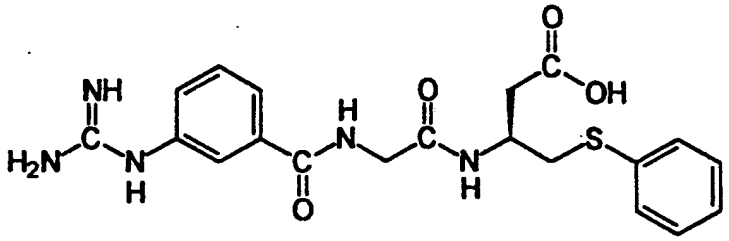


.TFA

A solution of the product from Example 63 (200 mg) in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with of m-chloroperoxybenzoic acid (460 mg). The reaction was stirred overnight at room temperature. The reaction was treated with LiOH (200 mg). After 2 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). 3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-[(4-methylphenyl)sulfonyl]pentanoic acid, trifluoroacetate salt (180 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 68

Preparation of 3S-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-(phenylthio)butanoic acid, trifluoroacetate salt



.TFA

Step A

A suspension of phenylmethyl 3S-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[(methylsulfonyl)-oxy]butanoate (3.9 g) [prepared according to U.S. 5,409,939], thiophenol (1.1 ml) and K_2CO_3 (1.4 g) in DMF (20 ml) was stirred at room temperature overnight. The reaction was treated with ethyl acetate and the organic layer was washed with H_2O (2 x 25 ml) and saturated NaCl (25 ml). The organic layer was dried with Na_2SO_4 and the excess solvent removed under reduced pressure to give a golden oil (4.5 g). The oil was dissolved in CH_2Cl_2 (100 ml) and treated with TFA (20 ml). After 4 hours the excess solvent was removed under reduced pressure and the product was purified by HPLC (RP-CH_3CN/H_2O). Phenylmethyl 3S-amino-4-(phenylthio)butanoate TFA salt (1.2 g) was isolated as a white solid. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (273 mg) and NMM (110 μl) in DMF (1 ml) was treated with pivaoyl chloride (120 μl). After 30 minutes, a solution of the product from Step A (208 mg), NMM (110

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/13500

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/55 A61K31/44 C07C279/18 A61K31/155 A61K31/36
C07D405/10 A61K31/395 C07D223/12 C07D401/14 C07D207/16
C07C275/28 A61K31/17 C07D401/10 C07D317/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 445 796 A (F.HOFFMANN-LA ROCHE) 11 September 1991 see page 7, line 37 - line 40; claim 1	1-58
E	WO 96 26190 A (SMITHKLINE BEECHAM) 29 August 1996 see claim 1	1-58
P,A	WO 96 00574 A (SMITHKLINE BEECHAM) 11 January 1996 see claim 1	1-58
A	EP 0 643 072 A (TAKEDA) 15 March 1995 see claim 1	1-58
A	WO 94 18981 A (MERCK & CO.) 1 September 1994 see page 28, line 22; claim 1	1-58

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 December 1996	23.01.1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/13500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-445796	11-09-91	CA-A- 2037153	10-09-91
		IL-A- 97401	15-03-95
		JP-B- 2501252	29-05-96
		JP-A- 4217652	07-08-92
		US-A- 5430024	04-07-95
		US-A- 5273982	28-12-93
		HR-A- 930353	30-06-96
WO-A-9626190	29-08-96	NONE	
WO-A-9600574	11-01-96	AU-A- 3001095	25-01-96
		WO-A- 9600730	11-01-96
EP-A-643072	15-03-95	AU-A- 6477194	22-12-94
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		HU-A- 70045	28-09-95
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		NO-A- 942274	19-12-94
		US-A- 5550131	27-08-96
WO-A-9418981	01-09-94	AU-A- 6246594	14-09-94
		BG-A- 99863	29-02-96
		CA-A- 2155123	01-09-94
		CN-A- 1118139	06-03-96
		CZ-A- 9502108	14-02-96
		EP-A- 0684823	06-12-95
		FI-A- 953916	21-08-95
		HU-A- 71796	28-02-96
		JP-T- 8507072	30-07-96
		NO-A- 953270	19-10-95
		PL-A- 310386	11-12-95

AN 1997:290093 CAPLUS
DN 126:264011
TI Preparation of meta-guanidine, urea, thiourea or azacyclic amino benzoic acid derivatives as integrin antagonists
IN Ruminski, Peter Gerrard; Clare, Michael; Collins, Paul Waddell; Desai, Bipinchandra Nanubhai; Lindmark, Richard John; Rico, Joseph Gerace; Rogers, Thomas Edward; Russell, Mark Andrew; et al.
PA G.D. Searle & Co., USA; Ruminski, Peter Gerrard; Clare, Michael; Collins, Paul Waddell; Desai, Bipinchandra Nanubhai; Lindmark, Richard, John
SO PCT Int. Appl., 930 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9708145	A1	19970306	WO 1996-US13500	19960827
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
	CA 2230209	AA	19970306	CA 1996-2230209	19960827
	AU 9671039	A1	19970319	AU 1996-71039	19960827
	AU 702487	B2	19990225		
	EP 850221	A1	19980701	EP 1996-932142	19960827
	EP 850221	B1	20010718		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	CN 1201454	A	19981209	CN 1996-197911	19960827
	CN 1085980	B	20020605		
	BR 9610422	A	19990713	BR 1996-10422	19960827
	JP 11510814	T2	19990921	JP 1996-510397	19960827
	IL 123164	A1	20010319	IL 1996-123164	19960827
	AT 203234	E	20010815	AT 1996-932142	19960827
	ES 2161373	T3	20011201	ES 1996-932142	19960827
	RU 2196769	C2	20030120	RU 1998-105408	19960827
	NO 9800817	A	19980424	NO 1998-817	19980226
	HK 1021532	A1	20020208	HK 1998-114666	19981228
PRAI	US 1995-3277P	P	19950830		
	WO 1996-US13500	W	19960827		

OS MARPAT 126:264011
AB The title compds. I [A = (un)substituted ureido, guanidino, etc. (generic structures given); Z1 = H, alkyl, OH, alkoxy, halo, (di)(alkyl)amino, aryl, etc.; V = NR6; R6 = H, alkyl, etc.; or YR6 forms a 4- to 12-membered [illegible]-N-contg. ring; Y, Y3, Z, Z3 = H, alkyl, aryl, cycloalkyl; or YZ or Y3Z3 form cycloalkyl; n = 1-3; t = 0-2; p = 0-3; R = XR3; X = O, S, NH, etc.; R3 = H, alkyl, etc.; R1 = H, alkyl, alkenyl, etc.; R11 = H, alkyl, aralkyl, etc.] are prepd. For example, m-nitrohippuric acid was subjected to a sequence of (1) amidation with Et 3-amino-3-(3-pyridyl)propanoate-2HCl; (2) hydrogenation of the nitro group; (3) reaction of the formed amine with benzyl isocyanate; and (4) alk. sapon. of the ester, to give title compd. II, isolated as the CF3CO2H or HCl salt. In an in vitro assay for antagonism of human vitronectin receptor (.alpha.V.beta.3), the title compd. II.HCl bound with an IC50 of 0.86 nM.
IT **188804-85-5P 188805-16-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of meta-guanidino, -ureido, -thioureido, or -azacyclic-amino benzoic acid derivs. as integrin antagonists)

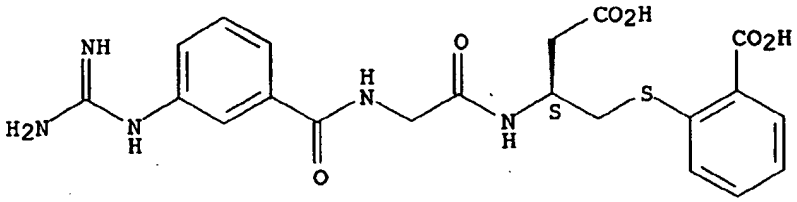
RN 188804-85-5 CAPLUS

CN Benzoic acid, 2-[[2-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]amino]-3-carboxypropyl]thio]-, (S)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

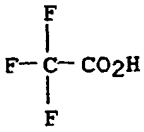
CRN 188804-84-4
CMF C21 H23 N5 O6 S

Absolute stereochemistry.



CM 2

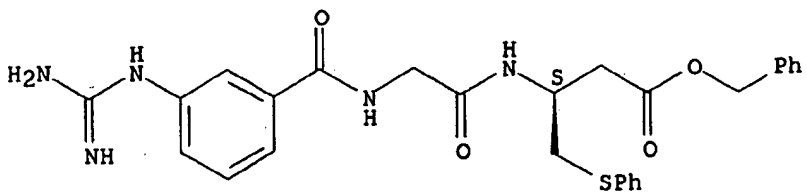
CRN 76-05-1
CMF C2 H F3 O2



RN 188805-16-5 CAPLUS

CN Butanoic acid, 3-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]amino]-4-(phenylthio)-, phenylmethyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

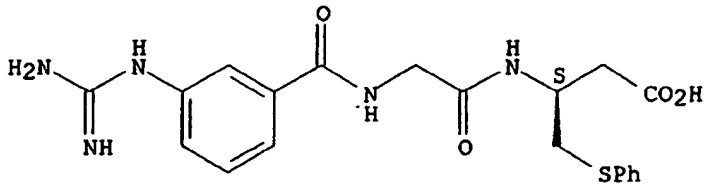


IT **188804-78-6P 188804-79-7P 188804-82-2P**

188804-83-3P 188804-84-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of meta-guanidino, -ureido, -thioureido, or -azacyclic-amino benzoic acid derivs. as integrin antagonists)

RN 188804-78-6 CAPLUS
CN Butanoic acid, 3-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]amino]-4-(phenylthio)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

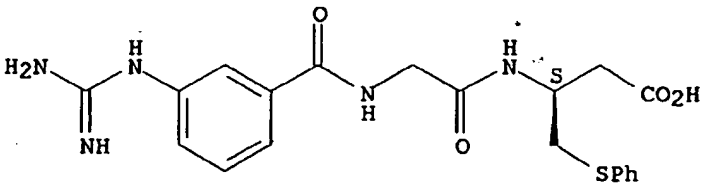


RN 188804-79-7 CAPLUS
CN Butanoic acid, 3-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]amino]-4-(phenylthio)-, (S)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

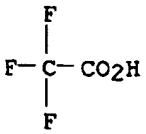
CRN 188804-78-6
CMF C20 H23 N5 O4 S

Absolute stereochemistry.



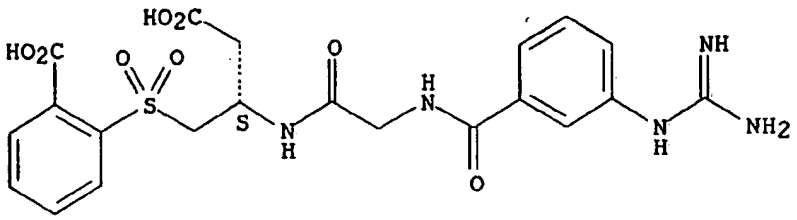
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 188804-82-2 CAPLUS
CN Benzoic acid, 2-[[2-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]am ino]-3-carboxypropyl]sulfonyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

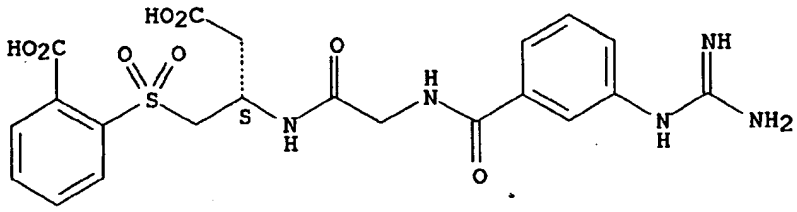


RN 188804-83-3 CAPLUS
CN Benzoic acid, 2-[[2-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]amino]-3-carboxypropyl]sulfonyl]-, (S)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

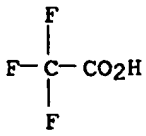
CRN 188804-82-2
CMF C21 H23 N5 O8 S

Absolute stereochemistry.



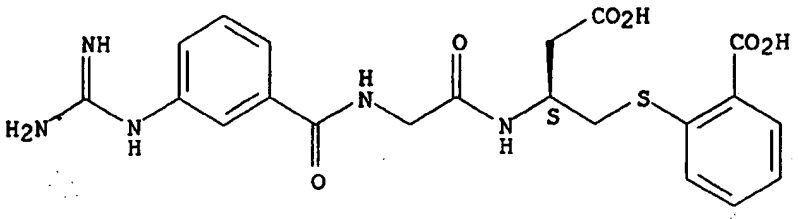
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 188804-84-4 CAPLUS
CN Benzoic acid, 2-[[2-[[[[3-[(aminoiminomethyl)amino]benzoyl]amino]acetyl]amino]-3-carboxypropyl]thio]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.


NH
H2N
N
H
O
H
N
O
N
H
S
CO2H
S
CO2H